



(18E1) 18E1

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Hewick, et al.

Serial No. : 07/800,364

Examiner: K. Furman

Filed : November 26, 1991

Art Unit: 1814

For : DNA ENCODING AND METHODS  
FOR PRODUCING BMP-8 PROTEINS

RECEIVED

DEC 11 1995

GROUP 1800

Honorable Commissioner of Patents  
and Trademarks  
BOX RECONSTRUCTION  
Washington, D.C. 20231

STATEMENT

In response to the request of September 20, 1995, attached is a copy of the Office Actions and Amendment papers. This affirms that to the best of my knowledge and belief, the attached list of papers (Appendix A) constitutes our records of the above-identified patent application insofar as it concerns the Patent and Trademark Office.

CERTIFICATE OF MAILING

Respectfully submitted,

Date of Deposit November 15, 1995  
I hereby certify that this correspondence is being deposited with the U.S. Postal Service under 37 CFR §1.8 as first class mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, BOX RECONSTRUCTION, Washington, D.C. 20231, on the date of deposit as indicated above.

Diana Gentile

Ellen J. Kapinos  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney of Record

LEGAL AFFAIRS  
GENETICS INSTITUTE, INC.  
87 CambridgePark Drive  
Cambridge, Massachusetts 02140  
Telephone: (617) 498-8622  
Facsimile: (617) 876-5851  
Dated: November 15, 1995

APPENDIX A

1. Correspondence from Patent and Trademark Office requesting application papers for reconstruction dated September 20, 1995.
2. Correspondence from Patent and Trademark Office dated September 20, 1995, advising that the Amendment filed July 31, 1995, has been considered.
3. Letter to the Patent and Trademark Office dated September 8, 1995, enclosing a certified copy of PCT/US91/03388.
4. Submission of Issue Fee to Patent and Trademark Office dated August 11, 1995.
5. Petition Under 37 CFR §1.84(b) dated July 26, 1995, and Figure 1.
6. Amendment under 37 CFR §1.312 and Response to Requirement for Substitute Declaration dated July 26, 1995.
7. Notice of Allowability, Notice of Allowance and Issue Fee Due dated May 15, 1995.
8. Amendment dated January 30, 1995.
9. Advisory Action dated November 8, 1994.
10. Office Action dated April 7, 1994.
11. Communication from Patent and Trademark Office notifying withdrawal of abandonment dated February 9, 1994.
12. Amendment, Notice of Appeal, Response to Notice and Submission of Formal Drawings w/Form 948, Sequence Listing, Statement under §1.825(b) and (a) dated October 5, 1994.
13. Letter with enclosures to Patent and Trademark Office requesting Notice of Abandonment be withdrawn dated January 13, 1994.
14. Notice of Abandonment dated September 14, 1993.
15. Amendment, Declaration of Deposit Requirements with enclosures, Information Disclosure Statement dated August 4, 1993.
16. Office Action dated February 5, 1993.
17. Preliminary Amendment, Statement pursuant to 37 CFR §1.825(a), Statement pursuant to 37 CFR §1.821(f), and Sequence Listing dated November 11, 1992.

**APPENDIX A (continued)**

18. Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures dated August 12, 1992.
19. Recorded Assignment dated January 27, 1992.
20. Filing Receipt received March 15, 1992.
21. Response to Notice to File Missing Parts of Application under 37 CFR §1.53(d), Declaration and Power of Attorney dated January 24, 1992.
22. Notice to File Missing Parts of Application dated January 6, 1992.



(1)

UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
ASSISTANT SECRETARY AND COMMISSIONER  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

Date: September 20, 1995

Legal Affairs Dept.  
Genetics Institute, Inc.  
87 Cambridgepark Dr.  
Cambridge, MA 02140

App. Serial No: 07/800,364

Patent No.:

Inventor(s): Hewick et al.

Filed: 11/26/91

Title of Invention: **DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS**

We are unable to locate the file identified above. An exhaustive search has been made throughout the Patent and Trademark Office, but the file cannot be found. There fore, we would like to replace the lost file with an authentic duplicate.

We have obtained a copy of the original application papers from our security film and would appreciate the loan of your official record, or a legible copy thereof, of the Office Actions and Amendment Papers in order to complete this file. Please include a list of the papers and a sworn statement that the papers listed constitute your record of this application insofar as it concerns the Patent and Trademark Office.

Please direct your reply to:

U.S. Patent and Trademark Office  
Box Reconstruction  
Washington, D.C. 20231  
(703)308-9726

Dorothy Smith  
Certification Division



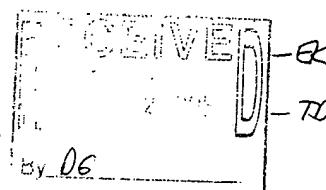
UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

(2)

SERIAL NUMBER	FILING DATE	FIRST NAME & LAST NAME	TYPE OF PAPER
07/800,364	11/26/91	HENICK	P 51820
		FURMAN, K.	EXAMINER
18M2/0920			
		ART. UNIT	PAPER NUMBER
		1814	
DATE MAILED/RECD			
11/26/91			

- A.  The petition filed \_\_\_\_\_ under 37 CFR 1.312(b) is granted.  
The paper has been forwarded to the examiner for consideration on the merits.



- B.  The amendment filed 7/31/95 under 37 CFR 1.312 has been considered, and has been:

1.  entered
2.  entered as directed to matters of form not affecting the scope of the invention (0.3311).
3.  disapproved. A report appears below.
4.  entered in part. A report appears below.

Report:

ROBERT A. WAX  
SUPERVISORY PATENT EXAMINER  
GROUP 180

PLEASE FURNISH YOUR ZIP CODE IN ALL CORRESPONDENCE

(3)

## CERTIFICATE OF MAILING

Date of Deposit

September 13, 1995

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail under 37 CFR §1.8 in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C., 20231, on the date of deposit as indicated above.

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rodney M. Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

For : DNA ENCODING AND METHODS  
FOR PRODUCING BMP-8 PROTEINS

September 8, 1995

Hon. Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

## LETTER

Enclosed is a certified copy of PCT/US91/03388.

Respectfully submitted,

Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
(617) 498-8622

Legal Affairs  
Genetics Institute, Inc.  
87 Cambridge Park Drive  
Cambridge, MA 02140

FILING DATE

15 MAY 1991

PCT/US 91/03388

SE	NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
	PCT/US91/03388	15 MAY 1991			ISA/ EP	

APPLICANT'S

GENETICS INSTITUTE, INC.

UNITED STATES OF AMERICA

525,357

16 MAY 1990

UNITED STATES OF AMERICA

641,204

15 JANUARY 1991

Foreign priority claimed 35 USC 119 conditions met	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	AS FILED	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
			→	025	1	16	8		GI 5132X-?

ADDRESS

ELLEN J. KAPINOS  
 LEGAL AFFAIRS  
 GENETICS INSTITUTE, INC.  
 87 CAMBRIDGE PARK DRIVE  
 CAMBRIDGE, MASSACHUSETTS 02140

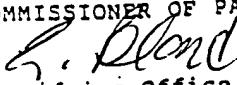
TITLE

BONE AND CARTILAGE INDUCTIVE PROTEINS

This is to certify that annexed hereto is a true copy of the above-identified International application as originally filed and any corrections thereto from the records of the United States Patent and Trademark Office acting as a Receiving Office under the Patent Cooperation treaty.

By authority of the

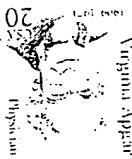
COMMISSIONER OF PATENTS AND TRADEMARKS

  
 Certifying Office

Date AUG 24 1995



Cambridge, MA 02140  
87 Cambridge Park Drive  
Legal Affairs  
Inc.



### PATENT

Serial No. 07/600,364 Doc. No. 615152A Atty/Sec EK/DL Date Sept 13, 1995

Inventor Rodney M. Hewick et al

Title DNA Encoding and Methods for Producing BMP-S Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

- pp. Spec.,  claims (1- ),  Abstract  pp. Preliminary Amendment
- pp. Sequence ID Listing/Computer Diskette  pp. Amendment/Response
- pp. Statement re Sequence ID Listing  pp. Declaration/Exhibits
- pp. Declaration/Power of Attorney  pp. Transmittal Letter (triplicate)
- shts. Informal/Formal Drawings  42 15  pp. Appeal Brief (triplicate)
- pp. Assignment & Fee  Issue Fee
- pp. Extension of Time & Fee (duplicate)  Notice of Appeal & Fee
- pp. Information Disclosure Statement & Fee  copy of PCT / US 91/03358  
with PTO-1449 and  references



The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Respectfully,  
Genetics Institute, Inc.

### PATENT

Express Mail Label No. \_\_\_\_\_

Serial No. 07/600,364 Dc

Inventor Rodney M. Hewick et al

Title DNA Encoding and Methods for Producing BMP-S Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

- pp. Spec.,  claims (1- ),  Abstract  pp. Preliminary Amendment
- pp. Sequence ID Listing/Computer Diskette  pp. Amendment/Response
- pp. Statement re Sequence ID Listing  pp. Declaration/Exhibits
- pp. Declaration/Power of Attorney  pp. Transmittal Letter (triplicate)
- shts. Informal/Formal Drawings  pp. Appeal Brief (triplicate)
- pp. Assignment & Fee  Issue Fee
- pp. Extension of Time & Fee (duplicate)  Notice of Appeal & Fee
- pp. Information Disclosure Statement & Fee  copy of PCT / US 91/03358  
with PTO-1449 and  references

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Respectfully,  
Genetics Institute, Inc.

Express Mail Label No. \_\_\_\_\_

(4)

CERTIFICATE OF EXPRESS MAILING

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Date of Deposit August 11, 1995

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Diana Gentile

GI-5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit: 1814

Examiner: K. Furman

Applicant: Rodney M. Hewick et al.

Issue Batch: L54

Serial No.: 07/800,364

Date of Allowance: May 15, 1995

Filed: November 26, 1991

For: DNA ENCODING AND METHODS  
FOR PRODUCING BMP-8 PROTEINS

August 11, 1995

Hon. Commissioner of Patents

and Trademarks

BOX ISSUE FEE

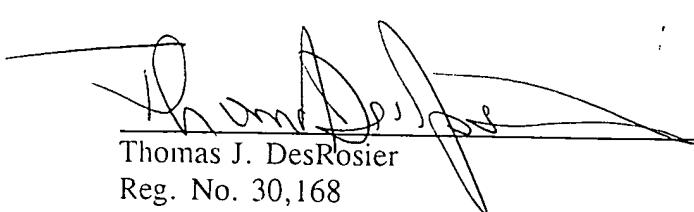
Washington, D.C. 20231

SUBMISSION OF ISSUE FEE

Applicants submit herewith authorization and appropriate forms PTOL-85b and PTOL-85c for charging the Issue Fee and any other fees that may be due in this case to Deposit Account No. 07-1060.

As indicated in the Notice, the deadline for submitting the Issue Fee is August 15, 1995. This response should therefore be deemed timely filed.

Respectfully submitted,

  
Thomas J. DesRosier  
Reg. No. 30,168  
Attorney for Applicants

LEGAL AFFAIRS  
GENETICS INSTITUTE, INC.  
87 CambridgePark Drive  
Cambridge, MA 02140  
Telephone: (617) 498-8622  
Telefax: (617) 876-5851

**PART B—ISSUE FEE TRANSMITTAL**

**MAILING INSTRUCTIONS:** This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to addressee entered in Block 1 unless you direct otherwise, by: (a) specifying a new correspondence address in Block 3 below; or (b) providing the PTO with a separate "FEE ADDRESS" for maintenance fee notifications with the payment of Issue Fee or thereafter. See reverse for Certificate of Mailing.

1. CORRESPONDENCE ADDRESS		2. INVENTOR(S) ADDRESS CHANGE (Complete only if there is a change)	
<p style="text-align: right;">18M2/0515</p> <p>LEGAL AFFAIRS DEPT. GENETICS INSTITUTE, INC. 87 CAMBRIDGE PARK DR. CAMBRIDGE, MA 02140</p>		INVENTOR'S NAME	
		Street Address	
		City, State and ZIP Code	
		CO-INVENTOR'S NAME	
		Street Address	
		City, State and ZIP Code	
<input type="checkbox"/> Check if additional changes are on reverse side			

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
97/000,364	11/26/91	004	FURMAN, K	1814 08/15/95

TITLE OF INVENTION: HEWICK, RODNEY M. DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS (AS AMENDED)

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEES DUE	DATE DUE
1	5192A	435-240-200	L54	UTILITY	NO	\$1210.00	08/15/95

3. Correspondence address change (Complete only if there is a change)	4. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.
	1 <u>Ellen J. Kapinos</u>
	2 <u>Thomas J. DesRosier</u>
	3 _____

DO NOT USE THIS SPACE

5. ASSIGNMENT DATA TO BE PRINTED ON THE PATENT (print or type)	6a. The following fees are enclosed: <input checked="" type="checkbox"/> Issue Fee <input checked="" type="checkbox"/> Advance Order - # of Copies <u>10</u>
(1) NAME OF ASSIGNEE: <u>Genetics Institute, Inc.</u>	6b. The following fees should be charged to: DEPOSIT ACCOUNT NUMBER <u>07-1060</u> (ENCLOSE PART C) <input type="checkbox"/> Issue Fee <input type="checkbox"/> Advance Order - # of Copies _____ <input type="checkbox"/> Any Deficiencies in Enclosed Fees _____
(2) ADDRESS: (CITY & STATE OR COUNTRY) <u>Cambridge, Massachusetts 02140 U.S.A.</u>	The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

- A.  This application is NOT assigned.  
 Assignment previously submitted to the Patent and Trademark Office.  
 Assignment is being submitted under separate cover. Assignments should be directed to Box ASSIGNMENTS.

**PLEASE NOTE:** Unless an assignee is identified in Block 5, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

**Note:** The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

Vice President and Chief Patent Counsel

1. MAILING INVOICE WITH FEE CERTIFICATE OF MAILING ON REVERSE

## Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

Box ISSUE FEE  
Commissioner of Patents and Trademarks  
Washington, D.C. 20231

on August 11, 1995

(Date)

Diana Gentile  
(Name of person making deposit)

Diana Gentile  
(Signature)

August 11, 1995  
(Date)

Note: If this certificate of mailing is used, it can only be used to transmit the Issue Fee. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Office of Information Systems, Patent and Trademark Office, Washington, D.C. 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget, (Project 0651-0033), Washington, D.C. 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner of Patents and Trademarks, Box Issue Fee, Washington, DC 20231.

**PART C—CHARGE TO DEPOSIT ACCOUNT**

**1. CORRESPONDENCE ADDRESS**

18962, 0515

LEGAL AFFAIRS DEPT.  
GENETICS INSTITUTE, INC.  
87 FAMPTON PARK DR.  
CAMBRIDGE, MA 02140

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
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First Named Applicant	1062-0515-11/27/95	004	PLUMMER, M	10/26/95
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**TITLE OF  
INVENTION**

AN ENZYME ASSAY FOR PROBLEMS WITH ANTI-HER2  
ANTIBODIES

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEES DUE	DATE DUE
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**2a. The following fees are enclosed:**

Issue Fee       Advance Order - # of Copies \_\_\_\_\_

**2b. The following fees should be charged to:**

DEPOSIT ACCOUNT NUMBER 07-1060

Issue Fee       Advance Order - # of Copies 10

Any Deficiencies in Enclosed Fees

The COMMISSIONER OF PATENTS AND TRADEMARKS is  
requested to apply the Issue Fee to the application identified above.

( Authorized Signature )

Thomas J. Desrosier

8/11/95

NOTE: The Issue Fee will not be accepted from anyone other than the  
applicant; a registered attorney or agent; or the assignee or other party  
in interest as shown by the records of the Patent and Trademark Office.

Vice President and Chief Patent Counsel

**PATENT**

Serial No. 07/800,364 Doc. No. GT 5182A Atty/Sec. EK/06 Date 8/11/95  
Inventor Rodney M. Henick et al.  
Title PAV Encoding and Methods for Producing BMP-8 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

- |  |  |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u>  </u> ), <input type="checkbox"/> Abstract       | <input type="checkbox"/> pp. Preliminary Amendment           |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette   | <input type="checkbox"/> pp. Amendment/Response              |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing  | <input type="checkbox"/> pp. Declaration/Exhibits            |
| <input type="checkbox"/> pp. Declaration/Power of Attorney   | <input type="checkbox"/> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings  | <input type="checkbox"/> pp. Appeal Brief (triplicate)       |
| <input type="checkbox"/> pp. Assignment & Fee  | <input checked="" type="checkbox"/> Issue Fee                |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate)   | <input type="checkbox"/> Notice of Appeal & Fee              |
| <input type="checkbox"/> pp. Information Disclosure Statement & Fee<br>with PTO-1449 and <input type="checkbox"/> references | <input type="checkbox"/>                                     |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card  
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Respectfully,  
Genetics Institute, Inc.

Express Mail Label No. BB 793 965 512 W

**PATENT**

Serial No. 07/800,364 Doc. No. GT 5182A Atty/Sec. EK/06 Date 8/11/95  
Inventor Rodney M. Henick et al.  
Title PAV Encoding and Methods for Producing BMP-8 Proteins

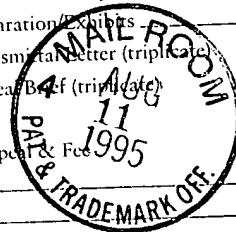
The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

- |  |  |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u>  </u> ), <input type="checkbox"/> Abstract       | <input type="checkbox"/> pp. Preliminary Amendment           |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette   | <input type="checkbox"/> pp. Amendment/Response              |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing  | <input type="checkbox"/> pp. Declaration/Exhibits            |
| <input type="checkbox"/> pp. Declaration/Power of Attorney   | <input type="checkbox"/> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings  | <input type="checkbox"/> pp. Appeal Brief (triplicate)       |
| <input type="checkbox"/> pp. Assignment & Fee  | <input checked="" type="checkbox"/> Issue Fee                |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate)   | <input type="checkbox"/> Notice of Appeal & Fee              |
| <input type="checkbox"/> pp. Information Disclosure Statement & Fee<br>with PTO-1449 and <input type="checkbox"/> references | <input type="checkbox"/>                                     |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card  
and place it in the outgoing mail.

Respectfully,  
Genetics Institute, Inc.

Express Mail Label No. BB 793 965 512 W



(5)

**CERTIFICATE OF MAILING**Date of Deposit July 26, 1995

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail under 37 CFR §1.8 in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date of deposit as indicated above.

*Ellen J. Kapinos*

GI 5182A

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants : Rodney M. Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

For : DNA ENCODING AND METHODS  
FOR PRODUCING BMP-8 PROTEINS

July 26, 1995

Hon. Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

**PETITION UNDER 37 C.F.R. §1.84(b)**

Sir:

In accordance with the provision of 37 C.F.R. §1.84(b), Applicants hereby Petition the Commissioner to accept and consider the attached Photograph (Figure 1) in the above-identified application. The Applicants are submitting in triplicate the photograph developed on double weight photographic paper.

Applicants respectfully request that the Petition fee under 37 C.F.R. §1.17(h) for One Hundred Thirty Dollars (\$130) be charged to our Deposit Account No. 07-1060. Three copies of this Petition are enclosed for bookkeeping purposes.

**SUBMITTED IN TRIPPLICATE**

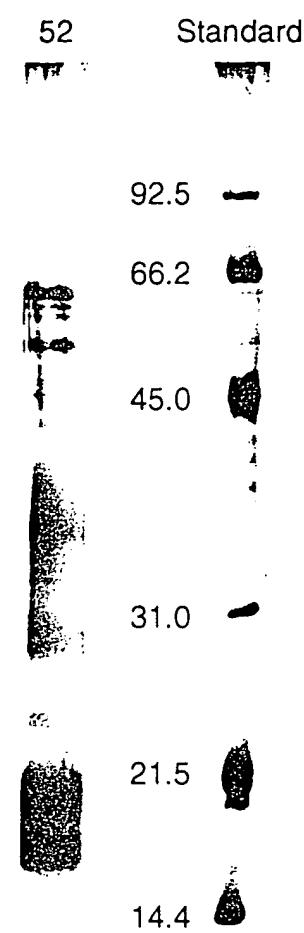
Respectfully submitted,

Date July 26, 1995

*Ellen J. Kapinos*  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
(617) 498-8622

Legal Affairs  
Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140

FIGURE 1



## PATENT

Serial No. 07/1800, 364 Doc. No. 5182A Atty/Sec ER/DG Date July 31, 1995  
Inventor Rodney M. Heuck et al  
Title DATA AND METHODS FOR PRODUCING BMP-8 PROTEINS

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

- |  |  |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u>  </u> ), <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Preliminary Amendment           |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette   | <input type="checkbox"/> pp. Amendment/Response              |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing  | <input type="checkbox"/> pp. Declaration/Exhibits            |
| <input type="checkbox"/> pp. Declaration/Power of Attorney   | <input type="checkbox"/> pp. Transmittal Letter (triplicate) |
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| <input type="checkbox"/> pp. Assignment & Fee  | <input type="checkbox"/> Issue Fee                           |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate)   | <input type="checkbox"/> Notice of Appeal & Fee              |

1.2 PTO-1449 UNDER §184(b)

## PATENT

Serial No. 07/1800, 364 Doc. No. 5182A Atty/Sec ER/DG Date July 31, 1995  
Inventor Rodney M. Heuck et al  
Title DATA AND METHODS FOR PRODUCING BMP-8 PROTEINS

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

- |  |  |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u>  </u> ), <input type="checkbox"/> Abstract | <input type="checkbox"/> pp. Preliminary Amendment           |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette   | <input type="checkbox"/> pp. Amendment/Response              |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing  | <input type="checkbox"/> pp. Declaration/Exhibits            |
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| <input type="checkbox"/> shts. Informal/Formal Drawings  | <input type="checkbox"/> pp. Appeal Brief (triplicate)       |
| <input type="checkbox"/> pp. Assignment & Fee  | <input type="checkbox"/> Notice of Appeal & Fee              |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate)   | <input type="checkbox"/> 1.2 PTO-1449 UNDER §184(b)          |
| <input type="checkbox"/> pp. Information Disclosure Statement (with PTO-1449 and <u>  </u> references)                 | <input type="checkbox"/> in triplicate                       |

1.2 PTO-1449 UNDER §184(b)  
its stamp on this postal card  
TO FORM 948

Inc.

1.2 PTO-1449 UNDER §184(b)

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*IP COPY OF PTO form 948*

Respectfully,  
Genetics Institute, Inc.

Express Mail Label No. \_\_\_\_\_

*Permit Rate of First Class  
Mail*

**CERTIFICATE OF FACSIMILE TRANSMISSION**

Date of Transmission July 31, 1995  
Telefax No. (703) 308-4227

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office on the date indicated above.

Ellen J. Kapinos

**CERTIFICATE OF MAILING**

Date of Deposit July 31, 1995

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Ellen J. Kapinos

GI 5182A

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants : Rodney M. Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

For : DNA ENCODING AND METHODS  
FOR PRODUCING BMP-8 PROTEINS

July 26, 1995

Hon. Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

AMENDMENT UNDER 37 C.F.R. §1.~~132~~<sup>312</sup> AND  
RESPONSE TO REQUIREMENT FOR SUBSTITUTE DECLARATION

Sir:

Further to the telephone conference with Examiner Furman May 17, 1995, please amend the application as follows:

In the Specification:

Page 35, line 27, after "hH38." and before DNA, insert --Clone hH38 was deposited with the American Type Culture Collection (ATCC), Rockville, Maryland, under the accession number 69778 on March 30, 1995.--

REMARKS

It is understood that this amendment to reference the deposit number of clone hH38 does not raise any new matter issues.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991  
Page 2

The Notice of Allowability mailed May 15, 1995, indicates that the declaration filed January 24, 1992, lacks signature of the inventors. It is submitted that the declaration filed January 24, 1992, does include the signatures of each of the inventors. A copy of the declaration and the postcard are enclosed.

It is understood, therefore, that substitute declaration is not necessary. If this understanding is not correct, Applicants request the Examiner to notify Applicants:

Respectfully submitted,

  
Ellen J. Kepinos  
Ellen J. Kepinos  
Reg. No. 32,245  
Attorney for Applicants  
(617) 498-8622

Legal Affairs  
Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rodney M. Hewick et al

Serial No.: 07/800,364

Filed : November 26, 1991

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 24, 1992

Hon. Commissioner of Patents  
and Trademarks  
Washington, DC 20231

RESPONSE TO NOTICE TO FILE MISSING PARTS  
OF APPLICATION UNDER 37 C.F.R. 1.53(d)

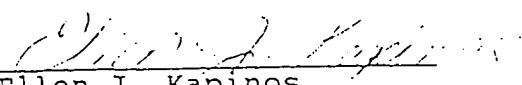
Sir:

In response to a Notice to File Missing Parts of Application under 37 C.F.R. Section 1.53(d) issued in connection with the above-identified application on January 6, 1992, Applicants hereby submit their Declaration and Power of Attorney pursuant to 37 C.F.R. Section 1.63.

The Declaration refers to the application's above-identified serial number and filing date. As indicated in the Notice, the deadline for submitting the Declaration is February 6, 1992.

Authorization is hereby given to charge the \$120 (One-hundred twenty dollar) surcharge under 37 C.F.R. Section 1.16(e) and any additional fees which may be required in this regard, and to credit any overpayment to Deposit Account No. 07-1060. Two duplicate copies of this letter are enclosed.

Respectfully submitted,

  
Ellen J. Kapinos  
Registration No. 32,245  
Genetics Institute, Inc.  
87 Cambridge Park Drive  
Cambridge, MA 02140-2387  
Phone (617) 876-1170  
Fax (617) 876-5851

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992.

I hereby certify that this correspondence is being  
mailed with the United States Postal Service in  
first class mail in an envelope addressed to Com-  
missioner of Patents and Trademarks, Washing-  
ton, D.C. 20231, on January 24, 1992  
See my 3 pages

Docket No. GI 5182

Declaration and Power of Attorney

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am ~~the original, first and sole inventor (if only one name is listed below)~~ or  
an original, first and joint inventor (if plural names are listed below) of the subject  
matter which is claimed and for which a patent is sought on the invention entitled:

BONE AND CARTILAGE INDUCTIVE PROTEINS

the specification of which: \_\_\_\_\_ is attached hereto.

X was filed on 11/26/91 as

Application Serial No. 07/800,364

and was amended on \_\_\_\_\_.

I hereby state that I have reviewed and understand the contents of the above-identified  
specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information of which I am aware which is material  
to the examination of this application in accordance with Title 37, Code of Federal  
Regulations, section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, section 119  
of any foreign application(s) for patent or inventor's certificate listed below and have  
also identified below any foreign application for patent or inventor's certificate having  
a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

<u>Number</u>	<u>Country</u>	<u>Day/Month/Year Filed</u>	<u>Priority Claimed</u>
PCT/US91/03388	designated:	15 May 1991	<u>Yes/No</u> Yes

I hereby claim the benefit under Title 35, United States Code, section 120 of any United  
States Application(s) listed below and, insofar as the subject matter of each of the  
claims of this application is not disclosed in the prior United States application in the  
manner provided by the first paragraph of Title 35, United States Code, section 112, I  
acknowledge the duty to disclose material information as defined in Title 37, Code of  
Federal Regulations, section 1.56(a) which occurred between the filing date of the prior  
application and the national or PCT international filing date of this application:

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
07/525,357	16 May 1990	Pending
07/641,204	15 January 1991	Pending

\*Austria, Belgium, Switzerland and Liechtenstein, Germany, France, United Kingdom,  
Italy, Luxembourg, Netherlands, Sweden, Denmark, Spain, Greece, Japan, and Canada

Declaration and Power of Attorney  
GI 5182A

I hereby appoint the following attorneys to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith, to file any International Applications which are based thereon under the provisions of the Patent Cooperation Treaty and to act on my behalf before the competent International Authorities: Bruce M. Eisen, Reg. No. 22,847; Thomas J. DesRosier, Reg. No. 30,168; Luann Cseri, Reg. No. 31,822; Ellen J. Kapinos, Reg. No. 32,245; and Patricia McDaniels, Reg. No. 33,194.

Address all correspondence to Legal Affairs Department, Genetics Institute, Inc., 87 Cambridge Park Drive, Cambridge, MA 02140. Telephone number: 617-876-1170.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Rodney M. Hewick

Inventor's signature R. M. Hewick

Citizenship GB Date: 1/24/92 Residence: 16 Woodcliffe Road  
Lexington, MA 02173  
USA

Post Office address (if different) \_\_\_\_\_

Full name of second joint inventor: Jack H. Wang

Inventor's signature J. H. Wang

Citizenship US Date: 1/24/92 Residence: 522 Lowell Street  
Lexington, MA 02173  
USA

Post Office address (if different) \_\_\_\_\_

Full name of third joint inventor: John M. Wozney

Inventor's signature John M. Wozney

Citizenship US Date: 1/24/92 Residence: 59 Old Bolton Road  
Hudson, MA 01749  
USA

Post office address (if different) \_\_\_\_\_

Full name of fourth joint inventor Anthony J. Celeste

Inventor's signature Anthony J. Celeste

Citizenship US

Date 1/24/92

Residence 86 Packard St., Hudson, MA 01749 USA

Post Office Address (if different) \_\_\_\_\_

Full name of fifth joint inventor \_\_\_\_\_

Inventor's signature \_\_\_\_\_

Citizenship \_\_\_\_\_ Date \_\_\_\_\_

Residence \_\_\_\_\_

Post Office Address (if different) \_\_\_\_\_

Full name of sixth joint inventor \_\_\_\_\_

Inventor's signature \_\_\_\_\_

Citizenship \_\_\_\_\_ Date \_\_\_\_\_

Residence \_\_\_\_\_

Post Office Address (if different) \_\_\_\_\_

PATENT

Serial No. 07/800,364 Doc. No. 5182A Atty/Sec EK/EZ Date 1/24/92  
Inventor Rodney M. Hewick et al  
Title Burn + Cartilage Inductive Proteins

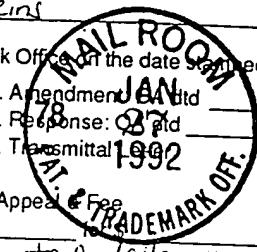
The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

- 3 pp. Spec., \_\_\_ Claim, \_\_\_ Abstract  
 pp. Declaration/Power of Attorney  
 pp. Verified Statement (Small Entity)  
 shs. Informal Drawings  
 shs. Formal Drawings  
 pp. Assignment  
 pp. Preliminary Amendment  
 pp. Extension of Time  
 pp. Information Disclosure Statement  
with PTO-1499 and \_\_\_ references
- pp. Amendment 1A filed 1/24/92  
 pp. Response: Q filed 1/24/92  
 pp. Transmittal 1A filed 1/24/92  
 Issue Fee  
 Notice of Appeal Fee  
 Check # 1000 filed 1/24/92  
 Transmitted letter in triplicate  
 Copy of Notice to file missing parts

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Sent via First Class mail

Respectfully,  
Genetics Institute, Inc.



**PATENT**

Serial No. 07/180,364 Doc. No. 5182A Atty/Sec E.K / D.E Date July 31, 1995  
Inventor Rodney M. Hewick et al  
Title DNA Encoding and Methods for Producing

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

pp. Spec., claims (1- ), Abstract

- pp. Preliminary Amendment
- pp. Amendment/Response
- pp. Declaration/Exhibits
- pp. Transmittal Letter (triplicate)
- pp. Appeal Brief (triplicate)

Issue Fee

Notice of Appeal & Fee  
*2 pp Amendment 5.182A*  
Response to Requirement for  
Signature Declaration  
is fully requested to place its stamp on this postal card

Respectfully,  
Genetics Institute, Inc.

*(att) file # 116123  
M.J.I.*

**PATENT**

Serial No. 07/180,364 Doc. No. 5182A Atty/Sec E.K / D.E Date July 31, 1995  
Inventor Rodney M. Hewick et al  
Title DNA Encoding and Methods for Producing

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

- pp. Spec., claims (1- ), Abstract
- pp. Sequence ID Listing/Computer Diskette
- pp. Statement re Sequence ID Listing
- pp. Declaration/Power of Attorney
- shts. Informal/Formal Drawings
- pp. Assignment & Fee
- pp. Extension of Time & Fee (duplicate)
- pp. Information Disclosure Statement & Fee with PTO-1449 and references

- pp. Preliminary Amendment
- pp. Amendment/Response
- pp. Declaration/Exhibits
- pp. Transmittal Letter (triplicate)
- pp. Appeal Brief (triplicate)
- Issue Fee

Notice of Appeal & Fee

*2 pp Amendment 5.182A  
Response to Requirement for  
Signature Declaration*

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

*SPP attachments  
Respectfully,  
Genetics Institute, Inc.*

Express Mail Label No. \_\_\_\_\_

*Certificate of Service  
M.J.I.*

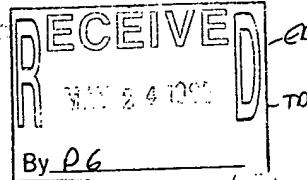




UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS,  
Washington, D.C. 20231

(7)

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
---------------	-------------	-----------------------	---------------------



NOTICE OF ALLOWABILITY

8/15/95 IF / formal Drawings / Decl.

PART I.

- This communication is responsive to Amend D, 1-131-35.
- All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
- The allowed claims are 7, 8, 14 and 15.
- The drawings filed on \_\_\_\_\_ are acceptable.
- Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [ ] been received. [ ] not been received. [ ] been filed in parent application Serial No. \_\_\_\_\_, filed on \_\_\_\_\_.
- Note the attached Examiner's Amendment.
- Note the attached Examiner Interview Summary Record, PTOL-413.
- Note the attached Examiner's Statement of Reasons for Allowance.
- Note the attached NOTICE OF REFERENCES CITED, PTO-892.
- Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

- Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED. *1-131-35*
- APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
  - Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. 1-131-35. CORRECTION IS REQUIRED.
  - The proposed drawing correction filed on \_\_\_\_\_ has been approved by the examiner. CORRECTION IS REQUIRED.
  - Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
  - Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- Examiner's Amendment
- Examiner Interview Summary Record, PTOL-413
- Reasons for Allowance
- Notice of References Cited, PTO-892
- Information Disclosure Citation, PTO-1449
- Notice of Informal Application, PTO-152
- Notice re Patent Drawings, PTO-948
- Listing of Bonded Draftsmen
- Other *Copy of PTO-152*

KEITH C. FURMAN  
PRIMARY EXAMINER  
GROUP 1800



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address: Box ISSUE FEE  
COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

18M2/0515

LEGAL AFFAIRS DEPT.  
GENETICS INSTITUTE, INC.  
10 CAMPBELL PARK DR.  
CAMBRIDGE, MA 02140

NOTICE OF ALLOWANCE  
AND ISSUE FEE DUE

- Note attached communication from the Examiner  
 This notice is issued in view of applicant's communication filed \_\_\_\_\_

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
67-17700-1000	11/20/1980	10	PTO/Office of Small Business	18M2/0515
First Named Applicant	MICHAEL J. KELLY			
TITLE OF INVENTION	DNA ENCODING AND METHODS FOR PRODUCING HUMAN PROTEINS (AN AMENDMENT)			
ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY

**THE APPLICATION IDENTIFIES ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT.  
PROSECUTION ON THE MERITS IS CLOSED.**

**THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS  
APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.**

**HOW TO RESPOND TO THIS NOTICE:**

- I. Review the SMALL ENTITY Status shown above.  
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
  - A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
  - B. If the Status is the same, pay the FEE DUE shown above.
  
- II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.
  
- III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
- B. File verified statement of Small Entity Status before, or with, pay of 1/2 the FEE DUE shown above.

**IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS,  
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKETT NO.
---------------	-------------	-----------------------	----------------------

EXAMINER

ART UNIT

PAPER NUMBER

DATE MAILED:  
*28*

**EXAMINER INTERVIEW SUMMARY RECORD**

All participants (applicant, applicant's representative, PTO personnel):

(1) *John Weyant* (3)

(2) *John F. Luria* (4)

Date of interview 2-23-95

Type:  Telephonic  Personal (copy is given to  applicant  applicant's representative).

Exhibit shown or demonstration conducted:  Yes  No. If yes, brief description:

Agreement  was reached with respect to some or all of the claims in question.  was not reached.

Claims discussed: *all pending*

Identification of prior art discussed: *none*

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: *left message for*

*the claims were allowed*

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

*[Signature]*  
Examiner's Signature

Date of Transmission Jan. 31, 1995 Telefax No. 1-703-308-4227

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office on the date indicated above.

Date of Deposit January 31, 1995

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(8)

GI 5182A

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS

WASHINGTON, D.C. 20231

ATTN: Application Processing Division

Special Processing and Correspondence Branch

Ellen J. Kapinos

SERIAL NO.: 07/800,364  
FILED: November 26, 1991  
GROUP ART UNIT: 1814

SIR:

In re application of: Rodney M. Hewick et al.

Entitled: DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS

Transmitted herewith is an Amendment (4 pages) in the above-identified application. The following checked items are applicable:

[ ] A Petition for Extension of Time for \_\_\_\_\_ months is hereby made, under §1.136(a) and the fee is calculated herein.

CLAIM TYPE	CLAIMS AFTER AMENDMENT MINUS PRIOR PAID CLAIMS	EQUALS PRESENT EXTRA CLAIMS	RATE	FEE
Independent	Z - 13	-	x \$76 =	\$0
Total	Z - 25	-	x \$22 =	0
[ ] Multiple Dependent Claims (1st presentation)			+\$240	0
			SUBTOTAL FEE	\$0
Fee for Petition for Extension				0
TOTAL FEE				\$0

[ ] The Commissioner is hereby authorized to charge payment of \$ \_\_\_\_\_ under §1.16 associated with this communication or credit any overpayment to Deposit Account No. 07-1060.

[X] No additional fee is believed due; however, if any fee should be due, authorization is hereby given to charge it to Deposit Account 07-1060.

SUBMITTED IN TRIPPLICATE

Respectfully submitted,

Ellen J. Kapinos

Ellen J. Kapinos  
Reg. No. 32,245  
Attorney of Record  
LEGAL AFFAIRS  
GENETICS INSTITUTE, INC.  
87 Cambridge Park Drive  
Cambridge, Massachusetts 02140  
Telephone: (617) 498-8622  
Facsimile: (617) 876-5851  
Dated: January 30, 1995

*CERTIFICATE OF FACSIMILE TRANSMISSION*

Date of Transmission

Jan 31, 1995 Telex No. 1-703-308-4227

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office on the date indicated above.

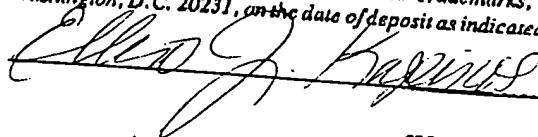


*CERTIFICATE OF MAILING*

Date of Deposit

January 31, 1995

I hereby certify that this correspondence is being deposited with the U.S. Postal Service under 37 CFR §1.8 in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date of deposit as indicated above.



GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rodney M. Hewick, et al.

Serial No. : 07/800,364

Filed : November 26, 1991

For : DNA ENCODING AND METHODS  
FOR PRODUCING BMP-8 PROTEINS

Art Unit: 1814

Examiner: K. Furman

January 30, 1995

Hon. Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

AMENDMENT

Sir:

This is in response to the Advisory Action mailed November 8, 1994, and the telephone conference with Examiner Furman January 5, 1995. Please amend the application as follows:  
In the Claims:

Cancel claims 6, 9, 13, 16-19, 26-33 and 35.

7. (third amendment) An isolated DNA sequence selected from the group consisting of  
[comprising]

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991  
Page 2

(a) the nucleotide sequence set forth in SEQ ID NO:13 [from] comprising nucleotide #8 to #850; and

(b) nucleotide sequences which encode the amino acid sequence comprising amino acid #139 to #142 of SEQ ID NO:14.

8. (third amendment) An isolated DNA sequence selected from the group consisting of [comprising]

(a) the nucleotide sequence set forth in SEQ ID NO:13 [from] comprising nucleotide #434 to #850; and

(b) nucleotide sequences which encode the amino acid sequence comprising amino acid #4 to #142 of SEQ ID NO:14.

#### REMARKS

Reconsideration of the application and entry of the amendments is requested. Claims 6, 9, 13, 16-19, 26-33 and 35 have been deleted in order to advance prosecution. By deletion of these claims, Applicants do not acquiesce in the outstanding rejections and reserve the right to pursue the subject matter of these claims in one or more continuing applications.

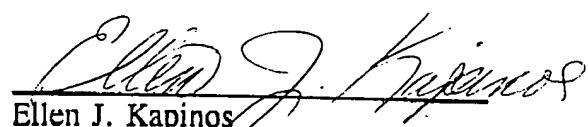
Claims 7 and 8 and 14 and 15 dependent thereon have been amended to include degenerate sequences as suggested by the Examiner. Basis for this amendment appears on page 6, lines 1-5 and 25-28 and page 10, lines 19-29. Claims 7, 8, 14 and 15 remain in the application and are set forth in attached Appendix A.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991  
Page 3

In view of the above, it is submitted that the claims as amended are in condition for allowance. Reconsideration of the rejections and objections is requested. Should the Examiner believe that a telephone interview would assist in clarifying any remaining issues, Applicants respectfully invite the Examiner to call the undersigned attorney at the telephone number provided below.

Respectfully submitted,

Date January 31, 1995

  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
(617) 498-8622

Legal Affairs  
Genetics Institute, Inc.  
87 Cambridge Park Drive  
Cambridge, MA 02140

## APPENDIX A

7. An isolated DNA sequence selected from the group consisting of
    - (a) the nucleotide sequence set forth in SEQ ID NO:13 comprising nucleotide #8 to #850; and
    - (b) nucleotide sequences which encode the amino acid sequence comprising amino acid #139 to #142 of SEQ ID NO:14.
  8. An isolated DNA sequence selected from the group consisting of
    - (a) the nucleotide sequence set forth in SEQ ID NO:13 comprising nucleotide #434 to #850; and
    - (b) nucleotide sequences which encode the amino acid sequence comprising amino acid #4 to #142 of SEQ ID NO:14.
14. A host cell transformed with the DNA of claim 7.
15. A host cell transformed with the DNA of claim 8.

**PATENT**

Serial No. 07/180,344 Doc. No. 5182 A Atty/Sec EK/DG Date 1-31-95

Inventor Rodney Itewick et al

Title DNA Encoding and Methods for Producing  
BMP-8 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon:

- |  |  |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u>  </u> ), <input type="checkbox"/> Abstract       | <input type="checkbox"/> pp. Preliminary Amendment                               |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette   | <input checked="" type="checkbox"/> <u>H</u> pp. Amendment/Response              |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing  | <input type="checkbox"/> pp. Declaration/Exhibits                                |
| <input type="checkbox"/> pp. Declaration/Power of Attorney   | <input checked="" type="checkbox"/> <u>I</u> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings  | <input type="checkbox"/> pp. Appeal Brief (triplicate)                           |
| <input type="checkbox"/> pp. Assignment & Fee  | <input type="checkbox"/> Issue Fee   |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate)   | <input type="checkbox"/> Notice of Appeal & Fee                                  |
| <input type="checkbox"/> pp. Information Disclosure Statement & Fee<br>with PTO-1449 and <input type="checkbox"/> references |  |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card  
and place it in the outgoing mail.

Respectfully,  
Genetics Institute, Inc.

**PATENT**

Serial No. 07/180,344 Doc. No. 5182 A Atty/Sec EK/DG

Inventor Rodney Itewick et al

Title DNA Encoding and Methods for Producing  
BMP-8 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon:

- |  |  |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> claims (1- <u>  </u> ), <input type="checkbox"/> Abstract       | <input type="checkbox"/> pp. Preliminary Amendment                               |
| <input type="checkbox"/> pp. Sequence ID Listing/Computer Diskette   | <input checked="" type="checkbox"/> <u>H</u> pp. Amendment/Response              |
| <input type="checkbox"/> pp. Statement re Sequence ID Listing  | <input type="checkbox"/> pp. Declaration/Exhibits                                |
| <input type="checkbox"/> pp. Declaration/Power of Attorney   | <input checked="" type="checkbox"/> <u>I</u> pp. Transmittal Letter (triplicate) |
| <input type="checkbox"/> shts. Informal/Formal Drawings  | <input type="checkbox"/> pp. Appeal Brief (triplicate)                           |
| <input type="checkbox"/> pp. Assignment & Fee  | <input type="checkbox"/> Issue Fee   |
| <input type="checkbox"/> pp. Extension of Time & Fee (duplicate)   | <input type="checkbox"/> Notice of Appeal & Fee                                  |
| <input type="checkbox"/> pp. Information Disclosure Statement & Fee<br>with PTO-1449 and <input type="checkbox"/> references |  |

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Washington, D.C. 20231

(9)

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/800,364	11/26/91	HEWICK	R 5182A

18MEZ/1108

LEGAL AFFAIRS DEPT.  
GENETICS INSTITUTE, INC.  
87 CAMBRIDGE PARK DR.  
CAMBRIDGE, MA 02140

FURMAN

PAPER NUMBER

1814

25

DATE

11/08/94

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

THE PERIOD FOR RESPONSE:

- a)  is extended to run \_\_\_\_\_ or continues to run \_\_\_\_\_ from the date of the final rejection  
b)  expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

Appellant's Brief is due in accordance with 37 CFR 1.192(a).

Applicant's response to the final rejection, filed 10-5-94 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1.  The proposed amendments to the claim and/or specification will not be entered and the final rejection stands because:  
a.  There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.  
b.  They raise new issues that would require further consideration and/or search. (See Note).  
c.  They raise the issue of new matter. (See Note).  
d.  They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.  
e.  They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE:

2.  Newly proposed or amended claims 9 and 35 would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3.  Upon the filing an appeal, the proposed amendment  will be entered  will not be entered and the status of the claims will be as follows:

Claims allowed: 7-9, 14, 15 and 35

Claims objected to: none

Claims rejected: 6, 13, 16-19 and 26-33

However;

Applicant's response has overcome the following rejection(s): The rejection set forth in Paragraph 5 is withdrawn

4.  The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because while the claims no longer read upon, cooperative species it would still require undue expenditure to determine what were active for the reasons previously discussed, which reasons have not been addressed by applicant. See also Grant Notice, 27 USPQ2d 1662 (GPO, 1993) which supports and/or supplements the technical analysis of claims by the Office in making any Notice or "Dissent" rejection, presented.

The proposed drawing correction  has  has not been approved by the examiner.

Other applicants are correct and thanked for noting that the omission of claim 28 from the scope of claim 26 was unintentional and/or it was, in fact, a typographical error as can be seen from the fact that the scope of the claims as in the other claims of the application. Keith K. Furman  
The formal drawings are not accepted for the reasons stated on the attached PTO-948.



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Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKETT NO.
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EXAMINER

ART UNIT	PAPER NUMBER
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24

DATE MAILED:

**EXAMINER INTERVIEW SUMMARY RECORD**

All participants (applicant, applicant's representative, PTO personnel):

(1) Ellen Kaganer (3) \_\_\_\_\_

(2) Cecilia Turner (4) \_\_\_\_\_

Date of Interview 10-3-94

Type:  Telephonic  Personal (copy is given to  applicant  applicant's representative).

Exhibit shown or demonstration conducted:  Yes  No. If yes, brief description: \_\_\_\_\_

Agreement  was reached with respect to some or all of the claims in question.  was not reached.

Claims discussed: none

Identification of prior art discussed: none

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Cecilia stated that

st. after final had been received.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

## NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftpersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date) 10-5-94 are  
 A. not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.  
 B. objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings:  
 Black ink. Color.  
 Not black solid lines. Fig(s) \_\_\_\_\_  
 Color drawings are not acceptable until petition is granted.
2. PHOTOGRAPHS. 37 CFR 1.84(b)  
 Photographs are not acceptable until petition is granted.
3. GRAPHIC FORMS. 37 CFR 1.84(d)  
 Chemical or mathematical formula not labeled as separate figure. Fig(s) \_\_\_\_\_  
 Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis. Fig(s) \_\_\_\_\_  
 Individuals waveforms not identified with a separate letter designation adjacent to the vertical axis. Fig(s) \_\_\_\_\_
4. TYPE OF PAPER. 37 CFR 1.84(e)  
 Paper not flexible, strong, white, smooth, nonshiny, and durable. Sheet(s) \_\_\_\_\_  
 Erasures, alterations, overwritings, interlineations, cracks, creases, and folds not allowed. Sheet(s) \_\_\_\_\_
5. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable paper sizes:  
 21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)  
 21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)  
 21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)  
 21.0 cm. by 29.7 cm. (DIN size A4)  
 All drawing sheets not the same size. Sheet(s) \_\_\_\_\_  
 Drawing sheet not an acceptable size. Sheet(s) \_\_\_\_\_
6. MARGINS. 37 CFR 1.84(g): Acceptable margins:  

Paper size			
21.6 cm. X 35.6 cm.	21.6 cm. X 33.1 cm.	21 cm. X 27.9 cm.	21 cm. X 29.7 cm.
(8 1/2 X 14 inches)	(8 1/2 X 13 inches)	(8 1/2 X 11 inches)	(DIN Size A4)
T .51 cm. (2")	.25 cm. (1")	.25 cm. (1")	.25cm.
L .64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	.25 cm.
R .64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.0 cm.
B .64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	

Margins do not conform to chart above.  
 Sheet(s) \_\_\_\_\_  
 Top (T) \_\_\_\_\_ Left (L) \_\_\_\_\_ Right (R) \_\_\_\_\_ Bottom (B) \_\_\_\_\_

## 7. VIEWS. 37 CFR 1.84(h)

REMINDER: Specification may require revision to correspond to drawing changes.

- All views not grouped together. Fig(s) \_\_\_\_\_
- Views connected by projection lines. Fig(s) \_\_\_\_\_
- Views contain center lines. Fig(s) \_\_\_\_\_
- Partial views. 37 CFR 1.84(h)(2)
  - Separate sheets not linked edge to edge. Fig(s) \_\_\_\_\_
  - View and enlarged view not labeled separately. Fig(s) \_\_\_\_\_
  - Long view relationship between different parts not clear and unambiguous. 37 CFR 1.84(h)(2)(ii)  
Fig(s) \_\_\_\_\_
- Sectional views. 37 CFR 1.84(h)(3)
  - Hatching not indicated for sectional portions of an object. Fig(s) \_\_\_\_\_
  - Hatching of regularly spaced oblique parallel lines not spaced sufficiently. Fig(s) \_\_\_\_\_
  - Hatching not at substantial angle to surrounding axes or principal lines. Fig(s) \_\_\_\_\_
  - Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s) \_\_\_\_\_
  - Hatching of juxtaposed different elements not angled in a different way. Fig(s) \_\_\_\_\_
- Alternate position. 37 CFR 1.84(h)(4)
  - A separate view required for a moved position. Fig(s) \_\_\_\_\_

ATTACHMENT TO PAPER NO. 25

Applicant's Copy

## Modified forms. 37 CFR 1.84(h)(5)

Modified forms of construction must be shown in separate views. Fig(s) \_\_\_\_\_

## 8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)

View placed upon another view or within outline of another. Fig(s) \_\_\_\_\_  
 Words do not appear in a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) \_\_\_\_\_

## 9. SCALE. 37 CFR 1.84(j)

Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s) \_\_\_\_\_  
 Indication such as "actual size" or "scale 1/2" not permitted. Fig(s) \_\_\_\_\_  
 Elements of view not in proportion to each other. Fig(s) \_\_\_\_\_

## 10. CHARACTER OF LINES, NUMBERS, &amp; LETTERS. 37 CFR 1.84(k)

Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings). Fig(s) \_\_\_\_\_

## 11. SHADING. 37 CFR 1.84(m)

Shading used for other than shape of spherical, cylindrical, and conical elements of an object, or for flat parts. Fig(s) \_\_\_\_\_  
 Solid black shading areas not permitted. Fig(s) \_\_\_\_\_

## 12. NUMBERS, LETTERS, &amp; REFERENCE CHARACTERS. 37 CFR 1.84(p)

Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(1) Fig(s) \_\_\_\_\_  
 Numbers and reference characters used in conjunction with brackets, inverted commas, or enclosed within outlines. 37 CFR 1.84(p)(1) Fig(s) \_\_\_\_\_  
 Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(1) Fig(s) \_\_\_\_\_  
 English alphabet not used. 37 CFR 1.84(p)(2) Fig(s) \_\_\_\_\_  
 Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s) \_\_\_\_\_

## 13. LEAD LINES. 37 CFR 1.84(q)

Lead lines cross each other. Fig(s) \_\_\_\_\_  
 Lead lines missing. Fig(s) \_\_\_\_\_  
 Lead lines not as short as possible. Fig(s) \_\_\_\_\_

## 14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(r)

Number appears in top margin. Fig(s) \_\_\_\_\_  
 Number not larger than reference characters. Fig(s) \_\_\_\_\_  
 Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s) \_\_\_\_\_

## 15. NUMBER OF VIEWS. 37 CFR 1.84(u)

Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) \_\_\_\_\_  
 View numbers not preceded by the abbreviation Fig. Fig(s) \_\_\_\_\_  
 Single view contains a view number and the abbreviation Fig. Fig(s) \_\_\_\_\_  
 Numbers not larger than reference characters. Fig(s) \_\_\_\_\_

## 16. CORRECTIONS. 37 CFR 1.84(w)

Corrections not durable and permanent. Fig(s) \_\_\_\_\_

## 17. DESIGN DRAWING. 37 CFR 1.152

Surface shading shown not appropriate. Fig(s) \_\_\_\_\_  
 Solid black shading not used for color contrast. Fig(s) \_\_\_\_\_

REVIEWER *[Signature]*

DATE 10-3-94



10

UNITED STATES DEPARTMENT OF COMMERCE  
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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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07/800,364 11/26/91 NEWTON

P 51826

EXAMINER

ETIRMAN, K

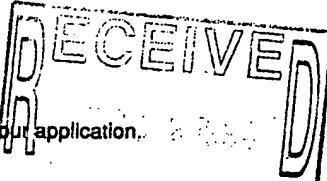
18M2/0407

ART UNIT

PAPER NUMBER

18

LEGAL AFFAIRS DEPT.  
GENETICS INSTITUTE, INC.  
87 CAMBRIDGE PARK DR.  
CAMBRIDGE, MA 02140



1814

DATE MAILED:

04/07/94

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined

Responsive to communication filed on

6/7/94 Final OA (and month) 7/13/94

-5K

-TD

7/7/94 Notice of Appeal (3rd m.)

This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

- Notice of References Cited by Examiner, PTO-892.
- Notice of Art Cited by Applicant, PTO-1449.
- Information on How to Effect Drawing Changes, PTO-1474.
- Notice of Draftsman's Patent Drawing Review, PTO-948.
- Notice of Informal Patent Application, PTO-152.
- \_\_\_\_\_

**Part II SUMMARY OF ACTION**

1.  Claims 1 - 35 are pending in the application.

Of the above, claims 1-5, 10-12 and 20-25 and 34 are withdrawn from consideration.

2.  Claims \_\_\_\_\_ have been cancelled.

3.  Claims 7, 8, 14 and 15 are allowed.

4.  Claims 6, 9, 13, 16-19 and 26 - 33 and 35 are rejected.

5.  Claims \_\_\_\_\_ are objected to.

6.  Claims 34 are subject to restriction or election requirement.

7.  This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8.  Formal drawings are required in response to this Office action.

9.  The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are  acceptable;  not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10.  The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_. has (have) been  approved by the examiner;  disapproved by the examiner (see explanation).

11.  The proposed drawing correction, filed \_\_\_\_\_, has been  approved;  disapproved (see explanation).

12.  Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has  been received  not been received  been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_.

13.  Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the provisions of 37 C.F.R. 1.14(d). A certificate of mailing can be obtained by filing the appropriate paper with the Office.

**Part III DETAILED ACTION**

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §1.821(a) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 CFR §§ 1.821 through 1.825 as follows: This application does not conform exclusively to the requirements of §§ 1.821 through 1.825. The non-conforming material should be deleted (§ 1.821(b)). The bovine sequence of native BMP-8 set forth on p. 33 in Table 4, while identified with regard to the sequence differences from the human homolog with respect to SEQ ID NO: 14 on p. 32 and not required for examination, must either be deleted or, preferably, a new Sequence Listing and CRF must be provided including this sequence since the sequence is actually shown on p. 33 of the specification. All sequences actually shown should be in the Sequence Listing.

**RESPONSE TO AFFIRMATION OF RESTRICTION REQUIREMENT**

2. Applicant's election without traverse of Group II in Paper No. 15 is acknowledged.

Claims 1-5, 10-12 and 20-25 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Election was made without traverse in Paper No. 15.

While applicants state at the bottom of p. 10 of the instant amendment that claims 1-5, 10-12 and 20-25 have been deleted, there is no specific amendment directing the cancellation of these claims and it is stated at the bottom of p. 11 that the claims are merely "withdrawn". Clarification is requested.

Newly submitted claim 34<sup>is</sup> directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The Invention of the instant DNAs, host cells and methods of producing BMP-8 proteins and the invention of

new claim 34 directed to a method for isolating a DNA sequence (separately classified in Class 435, subclass 6) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the products can be used to produce the BMP-8 protein for use as a drug.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 34 is also withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

#### OBJECTIONS/REJECTIONS WITHDRAWN

3. The specification is objected to under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 24 of the last Office Action, is withdrawn in view of the instant amendments and applicants' arguments.

The rejection of Claims 17 and 18 under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 26 of the last Office Action, is withdrawn in view of the instant amendments.

The objection to the specification and rejection of claims 9 and 18 under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 27 and 28 of the last Office Action, is withdrawn in view of the instant Declaration of Deposit Requirement including the required statements by the attorney of record.

The rejection of Claims 6-8, 13-15 and 19 under 35 U.S.C. § 112, second paragraph, as set forth in paragraph 29 of the last Office Action, is withdrawn in view of the instant amendments.

The rejection of Claims 6, 9, 13 and 16 under 35 U.S.C. § 101, as set forth in paragraph 32 of the last Office Action, is withdrawn in view of the instant amendments and applicants' arguments.

#### **NEW OBJECTIONS/REJECTIONS**

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 9, 16, 18 and 35 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 and those dependent thereon are indefinite and/or not enabled because that deposited as ATCC #75010 and #75011 are microorganisms having numerous DNAs and it is unclear which DNA applicants are referring to. The specification does not enable how to make and use the broad scope of all isolated DNAs of the deposited microorganism because the function of such DNAs and the proteins encoded is not disclosed or supported with respect to how to make and use them without undue experimentation. Additionally, claim 18 now expectedly reads upon a significant number of inoperative species because those skilled in the art would question whether the proteins encompassed in general would have the useful activity of the native BMP-8 protein having the native sequence for the reasons

previously discussed. Broad claim may be rejected merely because it reads on a significant number of inoperative species when examiner sets forth reasonable grounds in support of his or her conclusions that the claims may read upon inoperative subject matter and it becomes incumbent upon applicant either to reasonably limit claims to approximate area where operativeness has not been challenged or to rebut examiner's challenge by submission of representative evidence or by persuasive arguments based on known laws of physics and chemistry (see In re Cook and Merigold, 169 USPQ 298 (CCPA 1971)).

6. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 17-19, 26, 27 and 33 rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent 4,886,747 of Derynck et al. (AS). Derynck (cited by applicants after the first action) discloses the recombinant expression of TGF- $\beta$  comprising culturing a cell transformed with a vector comprising a DNA encoding TGF- $\beta$  in operative association with expression control sequences an the recovery, isolation and purification of the protein encoded by the DNA from the culture media (see Example 5). While Derynck et al. did not disclose the DNAs or proteins of the claims, claims 17-19, 26, 27 and 33 are drawn to the use of a new but similar product in an old process

of making which is not a patentably different process because the only difference between the process known in the art and the claimed process is the new product of applicants' claimed invention which would have been expected to work in the known process. See In re Durden 226 U.S.P.Q. 359 (Fed. Cir. 1985) and Ex parte Ochiai, 24 USPQ2d 1265 (BPAI, 1992). See also columns 19-21 of Kuberanpath et al. (AT) and col. 33 of Parsons et al. (which references are not required and not relied upon in the rejection but cited as further evidence) which further show that sequences of the family of proteins to which the instant sequence(s) belongs would have been expected to work in the known process, especially in view of the known homology between the members of this family and TGF- $\beta$ .

#### OBJECTIONS/REJECTIONS MAINTAINED

7. Applicant's arguments filed 1-13-93 have been fully considered but they are not deemed to be persuasive.

8. The rejection of Claims 6, 13 and 17 (now Claims 6, 13, 17, 29-33 and 35) under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to where the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2, as set forth in paragraph 25 of the last Office Action is again made and maintained.

Applicants' arguments are on the grounds that the limitation to include all of a), b) and c) which form part of the nucleotide sequence of BMP-8 should be enabled and obviate the rejection. However, these arguments are not persuasive because this is not what the Examiner had set forth as being enabled and applicants have not addressed the Examiner's arguments with regard to why that which is now claimed should be enabled in spite of those arguments. Further, the sequences of the claim are not known to be particularly correlated with the activity of the intact protein and it has not been shown that a protein merely containing these portions would have the requisite activity.

Additionally, even if such correlation and activity were shown, those skilled in the art would question whether these sequences in any order would produce an active protein due to possible steric hindrances, improper folding and/or incorrect juxtapositioning of critical regions. The limitations to include molecular weight limits does not narrow the scope so as not to require undue experimentation since the intervening portions which are not in the required portions (which can be any sequence) still encompasses an extremely large or essentially infinite number of species combinations and includes regions which may be required for useful activity. Additionally, claim 17 now expectedly reads upon a significant number of inoperative species because those skilled in the art would question whether the proteins encompassed in general would have the useful activity of the native BMP-8 protein having the native sequence for the reasons previously discussed.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. Claims 7, 8, 14 and 15 are allowed.

11. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE

EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Papers relating to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April 6, 1994

*Keith Furman*  
KEITH C. FURMAN, Ph.D.  
PRIMARY EXAMINER  
GROUP 1800



(11)

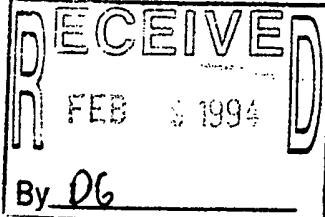
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Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/300,364	11/26/91	HEWLETT	R 51002

LEGAL AFFAIRS DEPT.  
GENETICS INSTITUTE, INC.  
87 CAMBRIDGE PARK DR.  
CAMBRIDGE, MA 02140

18M2/0207



EXAMINER	
F. WILKINSON	
ART UNIT	PAPER NUMBER
DATE MAILED:	
02/07/94	

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

The holding of abandonment mailed 9-14-93, has been withdrawn.

The copy of the response filed 8-4-93, has been made of record in the file.

The application has been returned to pending status.

  
Donna Chapman, Deputy Supervisory Application Examiner  
Patent Examining Group 1800

HONORABLE COMM: OWNER OF PATENTS AND TRADEMARKS  
WASHINGTON, D.C. 20231

SERIAL NO.: 07/800,364  
FILED: November 26, 1991  
GROUP ART UNIT: 1814

SIR:

In re application of: Rod Hewick et al.

Entitled: BONE AND CARTILAGE INDUCTIVE PROTEINS

Transmitted herewith is an Amendment in the above-identified application. The following checked items are applicable:

A Petition for Extension of Time for 3 months is hereby made, under §1.136(a) and fee is calculated herein;

Other: Notice of Appeal

Response to Notice and Submission of Formal Drawings w/ Form 948  
Sequence Listing, Dicrete, Statements Under 1.825 (b) and (g)

Claims after amendment	Minus Prior PAID claims	Equals present extra claims	RATE	Fee
Independent	- 13	=	x \$74.00 =	\$ .00
Total	- 25	=	x \$22.00 =	\$ .00
[ ] Multiple Dependent Claims (1st presentation)			+ \$230.00	\$ .00
<i>[XX] Notice of Appeal</i>			+ \$260.00	\$ 260.00
			SUBTOTAL FEE	\$ .00
<input checked="" type="checkbox"/> Petition for Extension of time fee pursuant to §1.17		extension within 3 months		\$870.00
			TOTAL ADDITIONAL FEE	\$1150.00

The fee has been calculated above; The Commissioner is hereby authorized to charge payment of \$1150.00 under §1.16 associated with this communication or credit any overpayment to Deposit Account No. 07-1060.

[ ] No additional fee is believed due.

CERTIFICATE OF MAILING "EXPRESS MAIL" NUMBER RB 793967900 US

Date of Deposit October 6 1991

I hereby certify that this correspondence is being deposited with the United States Postal Service Via Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on date indicated above and addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231.

*Ellen J. Kapinos*

*Ellen J. Kapinos*  
Attorney of Record: Ellen J. Kapinos  
Registration No. 32,245

SUBMITTED IN TRIPPLICATE

Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140

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Addressee" service under 37 CFR 1.10 on the date indicated below  
and is addressed to Honorable Commissioner of Patents and  
Trademarks, Washington, D.C. 20231 on October 5, 1994.

By Ellen J. Kapinos  
Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick et al.

Serial No. : 07/800,364 Examiner : K. Kurman

Filed : November 26, 1991 Art Unit : 1814

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

Hon. Commissioner of  
Patents and Trademarks  
Washington, DC 20231

PETITION AND FEE FOR EXTENSION OF TIME UNDER 37 CFR 1.136

We hereby request an extension of time for response of three (3) month/s pursuant to 37 CFR 1.136(a) in which to respond to the Office Action mailed April 7, 1994. This extension resets the time for response from July 7 to October 7, 1993.

We authorize the charging of Eight Hundred and Seventy (\$870.00) and any additional fees and crediting of overpayment to our Deposit Account 07-1060, and for this purpose, we enclose a duplicate copy of this petition.

Respectfully submitted,

October 4, 1994  
Date

Ellen J. Kapinos  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
(617)-876-1170  
Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140-2387

RESPONSE UNDER 37 CFR 1.116  
EXPEDITED PROCEDURE  
GROUP ART UNIT:1814

\*\*\*\*\*  
"Express Mail" mailing label number RB 793967900 US

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated below and is addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on October 5, 1994.

By Ellen J. Kapinos  
Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Hewick et al Group Art Unit: 1814

Serial No. : 07/800,364 Examiner: K. Furman

Filed : November 26, 1991

For : DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS

BOX AF  
Hon. Commissioner of Patents  
and Trademarks  
Washington, DC 20231

RESPONSE UNDER 37 CFR 1.116

Sir:

This is in response to the Office Action mailed April 7. A Request for a Three Month Extension and Fee accompanies this Response. The Extension resets the time for response from July 7 to October 7, 1994.

Please amend the application as follows:

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 2

In the Specification:

Page 32, line 7, after "Table 4" insert --(SEQ ID NO: 15)--.  
Page 33, line 23, after "Table 4" insert --(SEQ ID NO:15)--.  
Pages 41-48, delete the Sequence Listing and replace it with the enclosed Sequence Listing pages 41-53.

In the Claims:

Cancel claims 1-5, 10-12, 20-25, and 34.

6. (twice amended) An isolated DNA sequence encoding a BMP-8 protein comprising the following sequences

a)

GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC CAC (SEQ ID NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG  
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID NO: 11)

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 3

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

9. (twice amended) An isolated DNA comprising the [DNA] nucleotide sequence of ATCC #75010 encoding BMP-8.

17. (twice amended) A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

18. (twice amended) A method comprising the steps of

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 4

28. (once amended) An isolated DNA sequence encoding a BMP-8 protein comprising the following amino acid sequences:

a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:1);

b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

35. (once amended) An isolated DNA [sequence] comprising the nucleotide sequence of ATCC #75011 encoding BMP-8.

#### REMARKS

Reconsideration of the application and entry of the amendments is requested. The following documents accompany this response:

USSN 07/800, 364  
Filed Nov. 26, 1991  
GI 5182A  
Page 5

1. Transmittal Letter
2. Petition for Extension and Required Fee
3. Appendix A - Claims
4. Substitute Sequence Listing (pages 41-53)
5. Diskette containing computer readable Sequence Listing (CRF)
6. Statement Pursuant to 37 CFR 1.825(a) and 1.825(b)
7. Notice of Appeal
8. Drawing

A new Sequence Listing along with the CRF and statements in accordance with 37 CFR 1.821-1.825 are provided. The Sequence Listing has been amended to include the bovine sequence of BMP-8 set forth on page 33, Table 4 as SEQ ID NO: 15. The specification has been amended to reference SEQ ID NO:15. It is understood that the application now complies with the requirements of 37 CFR 1.821 through 1.825.

The application has been amended directing cancellation of claims 1-5, 10-12, 20-25, and 34 as these claims have been withdrawn from further consideration by the Examiner. Applicants hereby preserve their rights to pursue the subject matter contained in these withdrawn claims in one or more divisional applications filed pursuant to 35 U.S.C. 121. It is believed that the inventorship remains the same despite the withdrawal of non-elected claims. Claims 6, 9, 17, 18, 28 and 35 have been amended. The claims as amended appear in Appendix A.

Corrected formal drawings are submitted herewith.

WO 92/07073 cited as Foreign Patent Document "BM" on PTO form 1449 submitted with the amendment filed August 4, 1993 discloses an "OP-2" protein with sequence which corresponds to BMP-8 nucleotide and amino acid sequence.

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 6

Rejections Based on 35 USC §112

Claims 9, 16, 18 and 35 are rejected for lack of enablement and/or failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the Examiner, it is unclear which DNA of the deposited microorganisms is claimed. Claim 18 is further rejected for reading on inoperative species because one skilled in the art would question whether the proteins encompassed in general would have the useful activity of the native BMP-8 protein. Claim 9 and claims 16 and 18 dependent thereon and 35 have been amended to recite that the claimed sequence of the deposit is the nucleotide sequence encoding BMP-8. Basis for the amendments appears on page 34, lines 22-24 and page 28, lines 30 -32. Claim 18 has been further amended to characterize the recovered protein by the ability to induce the formation of cartilage and/or bone. It is understood that these claims are definite and enabling as they are directed to the BMP-8 sequence of the deposited microorganism. It is understood that claim 18 no longer reads on a significant number of inoperative species because step (b) is directed to the recovery of the protein encoded by the DNA of step (a) and having the functional limitation of the ability to induce cartilage and/or bone formation.

The rejection of claims 6,13 and 17 (now claims 6,13,17,29-33 and 35) because the disclosure is enabling only for claims limited to those wherein the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2, has been maintained. [In response Applicants have assumed that the Examiner intended

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 7

to include claim 28 in this grouping and request the Examiner to notify Applicants if this is not correct.] Claim 6 as amended recites a DNA encoding a BMP-8 protein comprising three sequences [a), b) and c)] which form part of the nucleotide sequence encoding BMP-8 and further recites the functional limitation of the recovered protein to induce the formation of cartilage and/or bone. Claim 28 has been similarly amended. It is submitted that the scope of claims 6, 28 and 13, 17, and 29-33 dependent thereon which are limited to a sequence comprising the sequences of a), b) and c) and encode a protein having the ability to induce the formation of cartilage and/or bone is reasonably correlated with the scope of enablement. Claim 17 has been further amended to include the characterization of the recovered protein by the ability to induce the formation of cartilage and/or bone. Therefore, it is submitted that claim 17 does not read on a significant number of inoperative species because those skilled in the art would be able to determine whether the recovered protein was active by its ability to induce cartilage and/or bone formation. It is therefore submitted that the claims are enabled by the disclosure.

Rejections Based on 35 USC §103

Claims 17-19, 26, 27 and 33 are rejected as unpatentable over Derynck et al., US 4,886,747. Derynck discloses the recombinant expression of TGF- $\beta$  comprising culturing a cell transformed with a vector comprising a DNA encoding TGF- $\beta$  and the recovery, isolation and purification of the protein. The Examiner contends that while Derynck et al. do not disclose the DNA or proteins of the present claims, claims 17-19, 26, 27 and

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 8

33 are drawn to the use of a new, but similar product in an old process of making. It is contended, based on In re Durden, 226 USPQ 359 (Fed. Cir. 1985) and Ex parte Ochiai, 24 USPQ2d 1265 (BPAI, 1992), that the present process is not patentable because the only difference is the new product of Applicant's claimed invention which would have been expected to work in the known process.

The court in Pleuddemann, 15 USPQ 2d 1738 (Fed. Cir. 1990) pointed out that the Durden court determined that the obviousness of a process is to be determined in light of the prior art, each case to be decided on the basis of its own fact situation (page 1741). The Pleuddemann court further pointed out that the claim appealed in Durden was for a method of making a compound. In Pleuddemann, the court found the §103 obviousness of the claims depended on the obviousness of using Appellant's new compounds which constitute the essential limitation of the claims, in light of the prior art. It concluded that the board's hindsight comparison of the functioning of the new compounds with the functioning of the compounds of the prior art was legal error. In upholding appellant's method of use claims it was found that appellant's specification teaching was used as though it were prior art in order to make claims to methods of bonding/priming using his admittedly novel compounds appear to be obvious.

In Ex parte Ochiai the board recognized the Pleuddemann distinction of the method of using claims wherein patentability is linked to patentability of material used and method of making novel material wherein patentability is determined based on inventiveness of process steps. The claims in Ochiai were found to be directed to a process of making and obvious.

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 9

Applicants have discovered a novel DNA sequence encoding a previously unknown protein. As the Examiner states, claims 17-19, 26, 27, and 33 are drawn to the use of a new product, in this case the DNA, which according to the Pleuddemann court the patentability thereof is linked to the patentability of the material used. In short, Applicants submit that these claims directed to the use of the novel DNA in a process for making the protein encoded by the DNA are patentable.

In view of the above, it is submitted that the claims as amended are in condition for allowance. Reconsideration of the rejections and objections is requested.

Should the Examiner believe that a telephonic interview would assist in clarifying any remaining issues or otherwise expedite prosecution, Applicants respectfully invite the Examiner to call the undersigned attorney at the telephone number provided below.

Respectfully submitted,

  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants

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87 CambridgePark Drive  
Cambridge, MA 02140

[ek]5182A.res

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 10

#### APPENDIX A

6. An isolated DNA sequence encoding a BMP-8 protein comprising the following sequences

a)  
GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC CAC (SEQ ID NO: 7);

b)  
GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG  
GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC  
ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)  
GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG  
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID NO: 11)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

7. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO:13 from nucleotide #8 to #850.

8. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO: 13 from nucleotide #434 through #850.

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 11

9. An isolated DNA comprising the nucleotide sequence of ATCC #75010 encoding BMP-8.

13. A host cell transformed with a DNA of claim 6.

14. A host cell transformed with the DNA of claim 7.

15. A host cell transformed with the DNA of claim 8.

16. A host cell transformed with the DNA of claim 9.

17. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

18. A method comprising the steps of

(a) culturing a cell transformed with a vector comprising

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 12

a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

19. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence comprising nucleotide #8 through #850 of SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and

(b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #4 to #142 of (SEQ ID NO:14).

26. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 13

27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

28. An isolated DNA sequence encoding a BMP-8 protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:1);
- b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and
- c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a

USSN 07/800, 364  
Filed Nov. 26, 1991  
GI 5182A  
Page 14

molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

33. A method comprising

a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and  
b) recovering, isolating and purifying from said culture medium a BMP-8 characterized by the following sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 15

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

35. An isolated DNA comprising the nucleotide sequence of ATCC #75011 encoding BMP-8.

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service under 37 CFR 1.10 on the date indicated below and is addressed to  
Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231  
on October 5, 1994.

By Ellen J. Kapinos  
Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Hewick et al	Group Art Unit: 1814
Serial No. : 07/800,364	Examiner : K. Furman
Filed : November 26, 1991	
For : DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS	

BOX AF  
Hon. Commissioner of Patents  
and Trademarks  
Washington, DC 20231

NOTICE OF APPEAL

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the decision dated April 7, 1994 of the Primary Examiner finally rejecting claims 6, 9, 13, 16-19, 26-33 and 35. Subsequent to Applicants' Request for Reconsideration and Amendment after Final under 37 CFR 1.116, filed herewith, currently pending claims are enclosed herewith as Appendix A to this Appeal.

A Petition for a Three Month Extension of Time and Fee are being filed herewith resetting the date for response from July 7 to October 7, 1994.

Applicants hereby authorize payment of two-hundred and seventy dollars (\$280.00) pursuant to 37 CFR 1.17(a) from Deposit Account No. 07-

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 2

1060. Although no additional fees are believed due, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment to Deposit Account No. 07-1060.

Respectfully submitted,



Ellen J. Kepinos  
Reg. No. 32,245  
Attorney for Applicants  
Tel: (617) 876-1170

Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140

SUBMITTED IN TRIPPLICATE

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 10

#### APPENDIX A

6. An isolated DNA sequence encoding a BMP-8 protein comprising the following sequences

a)

GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC CAC (SEQ ID NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG  
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID NO: 11)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

7. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO:13 from nucleotide #8 to #850.

8. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO: 13 from nucleotide #434 through #850.

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 11

9. An isolated DNA comprising the nucleotide sequence of ATCC #75010 encoding BMP-8.

13. A host cell transformed with a DNA of claim 6.

14. A host cell transformed with the DNA of claim 7.

15. A host cell transformed with the DNA of claim 8.

16. A host cell transformed with the DNA of claim 9.

17. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

18. A method comprising the steps of

(a) culturing a cell transformed with a vector comprising

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 12

a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

19. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence comprising nucleotide #8 through #850 of SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and

(b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #4 to #142 of (SEQ ID NO:14).

26. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 13

27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

28. An isolated DNA sequence encoding a BMP-8 protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:1);
- b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and
- c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 14

molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

33. A method comprising

a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and  
b) recovering, isolating and purifying from said culture medium a BMP-8 characterized by the following sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 15

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

35. An isolated DNA comprising the nucleotide sequence of ATCC #75011 encoding BMP-8.

"Express Mail" mailing label RB 793967900 US  
I hereby certify that this correspondence is being deposited with  
the United States Postal Service "Express Mail Post Office to  
Addressee" service under 37 CFR 1.10 on the date indicated below  
and is addressed to Honorable Commissioner of Patents and  
Trademarks, Washington, D.C. 20231 on October 5, 1994.

By Ellen J. Kapinos  
Ellen J. Kapinos

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick et al.

Serial No. : 07/800,364 Examiner : K. Kurman

Filed : November 26, 1991 Art Unit : 1814

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

Hon. Commissioner of  
Patents and Trademarks  
Washington, DC 20231

RESPONSE TO NOTICE AND SUBMISSION OF FORMAL DRAWINGS

Sir:

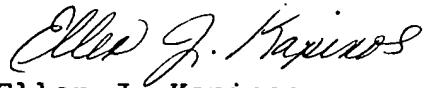
In response to the Notice of Draftsman's Drawing Review  
accompanying the Office Action mailed February 5, 1993,  
Applicants hereby submit 3 sheets of formal drawings to replace  
Figures 1 and 2.

Kindly substitute these formal drawings for the informal  
drawings currently on file. No new matter is presented by this  
submission.

USSN 07/800,364  
Filed Nov. 26, 1991  
GI 5182A  
Page 2

Should any fee be due, please charge any such fees associated with this request to Deposit Account 07-1060, and for that purpose, we enclose a duplicate copy of this petition.

Respectfully submitted,



Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
(617)-876-1170

Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140-2387

ATTACHMENT TO PAPER NUMBER

10

APPLICATION NUMBER

800 3601

GROUP 18 11

## NOTICE OF DRAFTSMAN'S PATENT DRAWING REVIEW

The PTO Draftsmen review all originally filed drawings regardless of whether they were designated as informal or formal.

The drawings filed 11/16/92

A.  are approved.

B.  are objected to under 37 CFR 1.84 for reason(s) checked below. The examiner will require submission of new, corrected drawings at the appropriate time. Corrected drawings must be submitted according to the instructions listed on the back of this Notice.

## 1. Paper and ink. 37 CFR 1.84(a)

- Poor Quality Paper. Must Be White.  
Transparent Paper Not Allowed.

Sheet(s) \_\_\_\_\_

## 2. Size of Sheet and Margins. 37 CFR 1.84(b)

## Acceptable Paper Sizes and Margins

## Paper Size

Margin	8 1/2 by 14 inches	8 1/2 by 13 inches	DIN size A4 21 by 29.7 cm.
Top	2 inches	1 inch	2.5 cm.
Left	1/4 inch	1/4 inch	2.5 cm.
Right	1/4 inch	1/4 inch	1.5 cm.
Bottom	1/4 inch	1/4 inch	1.0 cm.

Proper Size Paper Required. All Sheets Must be Same Size.

Sheet(s) \_\_\_\_\_

Proper Margins Required.

Sheet(s) \_\_\_\_\_

- Top       Right  
 Left       Bottom

## 3. Character of Lines. 37 CFR 1.84(c)

- Lines Pale, Rough and Blurred, or Jagged. Fig(s) \_\_\_\_\_

- Solid Black Shading Not Allowed. Fig(s) \_\_\_\_\_

4.  Photographs Not Approved.

Comments:

## 5. Hatching and Shading. 37 CFR 1.84(d)

- Shade Lines are Required.  
Fig(s) \_\_\_\_\_

- Criss-Cross Hatching Not Allowed.  
Fig(s) \_\_\_\_\_

- Double Line Hatching Not Allowed.  
Fig(s) \_\_\_\_\_

- Parts in Section Must be Hatched Properly. Fig(s) \_\_\_\_\_

## 6. Reference Characters. 37 CFR 1.84(f)

- Reference Characters Poor or Rough and Blurred. Fig(s) \_\_\_\_\_

- Minimum 1/8 inch (3.2 mm.) in height is required. Fig(s) \_\_\_\_\_

- Figure Legends Poor or Placed Incorrectly. Fig(s) \_\_\_\_\_

## 7. Views. 37 CFR 1.84(i) &amp; (j)

- Figures Must be Numbered Separately.

- Figures Must Not be Connected  
Fig(s) \_\_\_\_\_

## 8. Identification of Drawings. 37 CFR 1.84(l)

- Extraneous Matter or Copy Machine Marks Not Allowed. Fig(s) \_\_\_\_\_

- Changes Not Completed from Prior PTO-948 dated \_\_\_\_\_

Telephone inquiries concerning this review should be directed to the Chief Draftsman at telephone number (703) 557-6404.

2/20/92

Reviewing Draftsman

Date

FIGURE 1

52      Standard

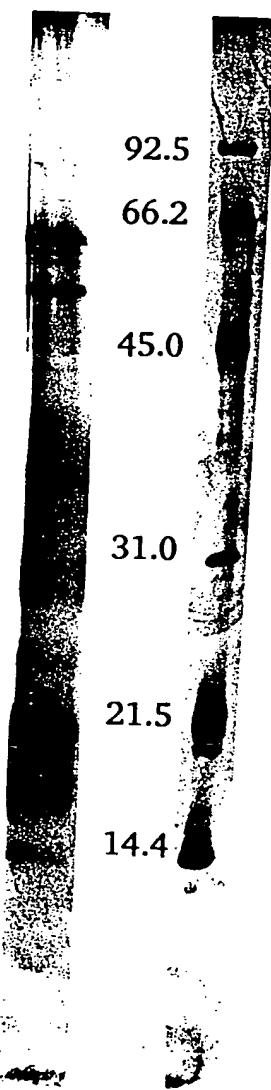


FIGURE 2

(1) GAATTCC GAG CCC CAT TGG AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC CCG GCT  
 Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala  
 (1)

GGG GAG GCG GTC ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG CCC AGC ATC CAC  
 Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His  
 (20)

CTG CTC AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG GTG GTC CAG GAG CAG TCC  
 Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser  
 (40)

AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT CTT CAG ACG CTC CGA GCT GGA GAC  
 Asn Arg Glu Ser Asp Leu Phe Leu Asp Leu Gln Thr Leu Arg Ala Gly Asp  
 (60)

GAG GGC TGG CTG GTG CTG GAT GTC ACA GCA GCC AGT GAC TGC TGG TTG CTG AAG  
 Glu Gly Tyr Leu Val Asp Val Leu Ala Ala Ser Asp Cyc Trp Leu Leu Lys  
 (80)

CGT CAC AAG GAC CTG GGA CTC CGC CTC TAT GTG GAG ACT GAG GAT GGG CAC AGC  
 Arg His Lys Asp Leu Gly Lue Arg Leu Tyr Val Glu Thr Glu Asp Gly His Ser  
 (90)

GTG GAT CCT GGC CTG GCC GGC CTG CTC GGT CAA CGG GCC CCA CGC TCC CAA CAG  
 Val Asp Pro Gly Leu Ala Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln  
 (110)

CCT TTG GTC ACT TTC TTC AGG GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG  
 Pro Phe Val Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg  
 (130)

(450) GCA GTG AGG CCA CTG AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG CCG CAG  
 Ala Val Arg Pro Leu Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln  
 (143)

(150)

(160)

FIGURE 2A

GCC AAC CGA CTC CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC CAC GGC CGG CAG  
Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly Arg Gln  
(170)

GTC TGC CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG GAC CTT GGC TGG CTG GAC  
Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp  
(180)

TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAG GGG GAG TGC TCC  
Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser  
(200)

TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG  
Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu  
(220)

GTC CAC CTG ATG AAG CCA AAC GCA GTC CCC AAG GCG TGC TGT GCA CCC ACC AAG  
Val His Leu Met Lys Pro Asn Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys  
(240)

CTG AGC GCC ACC TCT GTG CTC TAC TAT GAC AGC AGC AAC AAC GTC ATC CTG CGC  
Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg  
(260)

AAG CAC CGC AAC ATG GTG GTC AAG GCC TGC GGC TGC CAC TGAGTCAGCCCCAGC  
Lys His Arg Asn Met Val Val Lys Ala Cys Gly Cys His  
(280)

CCTACTGCAGGCCACCCCTTCTCATCTGGATCGGGCCCTGGAGGGCAGAAAACCCTTAATGCTGTCA  
(843)

CTCAAGCAGGAGTGTCAGGGGCCCTCACTCTGGTGCCTACTCTGGTGCAGGGCTTCTGGAAATT  
(270)

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

Title : BONE AND CARTILAGE INDUCTIVE PROTEINS

\*\*\*\*\*  
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 United States Postal Service as ~~first class~~<sup>4x2615</sup> mail in an envelope addressed  
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 D.C. 20231 on October 5, 1994.*

"Express Mail" number RB793967900US BY: *Ellen J. Kapines*

Hon. Commissioner of Patents  
 and Trademarks  
 Washington, D.C. 20231

## STATEMENT PURSUANT TO 37 CFR 1.825(a)

Pursuant to Part III of the Final Office Action dated April 7, 1994 received from the Patent and Trademark Office stating that the "Sequence Listing" does not comply with the requirements of §§1.821 through 1.825, a substitute and amended copy of the computer readable form of the Sequence listing which was duly submitted with the application as filed, is provided herewith.

Please substitute this amended Sequence Listing for the originally-filed Sequence Listing. The Sequence Listing and enclosed diskette now contain SEQ ID NOS:1-15.

This affirms that to the best of my knowledge and belief, these amendments present no substantive changes to the Sequence Listing and the computer readable copy of said Sequence Listing as originally filed. No new matter has been added.

Respectfully submitted,

October 4, 1994  
 Date

*Ellen J. Kapines*  
 Ellen J. Kapines  
 Reg. No. 32,245  
 Legal Affairs  
 Genetics Institute, Inc.  
 87 CambridgePark Drive  
 Cambridge, MA 02140  
 (617) 876-1170

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

Title : BONE AND CARTILAGE INDUCTIVE PROTEINS

\*\*\*\*\*  
*I hereby certify that this correspondence is being deposited with the  
United States Postal Service as ~~first class~~ mail in an envelope addressed  
to Honorable Commissioner of Patents and Trademarks, Washington,  
D.C. 20231 on October 5, 1994.*

"Express Mail" number RB793967900US BY:   
\*\*\*\*\*

Hon. Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

## STATEMENT PURSUANT TO 37 CFR 1.825(b)

Sir:

A substitute and amended copy of the computer readable form of the Sequence Listing which was duly submitted with the application, as filed, is provided herewith. This affirms that to the best of my knowledge and belief, the content of the substitute Sequence Listing and the computer readable copy of said Sequence Listing provided herewith are the same.

Respectfully submitted,

October 4, 1994  
Date

  
\_\_\_\_\_  
Ellen J. Kapinos  
Reg. No. 32,245  
Legal Affairs  
Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140  
(617) 876-1170

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

(i) APPLICANT: Hewick, Rodney M.  
Wang, Jack H.  
Wozney, John M.  
Celeste, Anthony J.

(ii) TITLE OF INVENTION: Bone and Cartilage Inductive Proteins

(iii) NUMBER OF SEQUENCES: 15

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Legal Affairs, Genetics Institute, Inc.  
(B) STREET: 87 CambridgePark Drive  
(C) CITY: Cambridge  
(D) STATE: MA  
(E) COUNTRY: USA  
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/800,364  
(B) FILING DATE: 26-NOV-1991  
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Kapinos, Ellen J.  
(B) REGISTRATION NUMBER: 32,245  
(C) REFERENCE/DOCKET NUMBER: GI 5182A

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617-876-1170  
(B) TELEFAX: 617-876-5851

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp  
 1           5           10           15

Val Ile Ala Pro Gln Gly Tyr  
 20

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile  
 1           5           10           15

Leu Arg

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ala Cys Cys Ala Pro Thr Lys  
1               5

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Thr Asn Glu Leu Pro Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp  
1               5               10               15

Val His Gly Ser His Gly Arg  
20

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 80 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:  
 (A) ORGANISM: *Bos taurus*

(vii) IMMEDIATE SOURCE:  
 (B) CLONE: acc30

(viii) POSITION IN GENOME:  
 (C) UNITS: bp

(ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 25..57

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GGATCCGCGT GCTGTGCTCC GACC AAG CTG AGC GCC ACC TCC GTG CTC TAC 51  
 Lys Leu Ser Ala Thr Ser Val Leu Tyr  
 1 5

TAC GAC AGCAGCAACA ATGTAATTCT AGA 80  
 Tyr Asp  
 10

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 11 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp  
 1 5 10

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 199 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Bos taurus

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Bovine genomic
- (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 30..199

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..29

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 30..179

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TGCCCGCTGC CCCCTCCCGC CCCCCGCCAG GTG CAC CTG CTG AAG CCG CAC GCG	53
Val His Leu Leu Lys Pro His Ala	
1                   5	

GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG	101
Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val	
10               15                   20	

CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC	149
Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn	
25               30               35                   40	

ATG GTG GTC CGC GCC TGC GGC TGC CAC TGAGGCCCA ACTCCACCGG	196
Met Val Val Arg Ala Cys Gly Cys His	
45               50	

CAG	199
-----	-----

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Val His Leu Leu Lys Pro His Ala Val Pro Lys Ala Cys Cys Ala Pro  
 1           5           10           15

Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn  
 20           25           30

Val Ile Leu Arg Lys His Arg Asn Met Val Val Arg Ala Cys Gly Cys  
 35           40           45

His

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 172 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

## (vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus

## (vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Bovine genomic
- (B) CLONE: Lambda 9800-10

## (viii) POSITION IN GENOME:

- (C) UNITS: bp

## (ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 51..161

## (ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..50

## (ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 162..172

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 51..161

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGGGTGGGAG GGCACGTGGA TGGGACTCAC CTTCTCCAC TACCCCCAG GAC TGG	56	
Asp Trp		
1		
GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC	104	
Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys		
5	10	15
TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG	152	
Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu		
20	25	30
CAG TCC CTG GTCAGTACCT C	172	
Gln Ser Leu		
35		

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly			
1	5	10	15
Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala			
20	25	30	
Ile Leu Gln Ser Leu			
35			

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 119 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:  
 (A) ORGANISM: Bos taurus

(vii) IMMEDIATE SOURCE:  
 (A) LIBRARY: Bovine genomic  
 (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:  
 (C) UNITS: bp

(ix) FEATURE:  
 (A) NAME/KEY: exon  
 (B) LOCATION: 20..99

(ix) FEATURE:  
 (A) NAME/KEY: intron  
 (B) LOCATION: 1..19

(ix) FEATURE:  
 (A) NAME/KEY: intron  
 (B) LOCATION: 100..119

(ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 22..99

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CCCTTGCAGTG TCCCCGCAGA C GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG        51  
 Asp Val His Gly Ser His Gly Arg Gln Val  
 1            5            10

TGC CGT CGG CAC GAG CTG TAC GTG AGC TTC CAG GAC CTG GGC TGG CTG        99  
 Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu  
 15            20            25

GTGAGTTCCG ACTCTCCTTT        119

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 26 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His Glu Leu  
 1           5           10           15

Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu  
 20           25

## (2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1003 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: circular

## (ii) MOLECULE TYPE: cDNA to mRNA

## (iii) HYPOTHETICAL: NO

## (vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
- (F) TISSUE TYPE: Human Heart

## (vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Human heart cDNA library stratagene catalog #936208
- (B) CLONE: hH38

## (viii) POSITION IN GENOME:

- (C) UNITS: bp

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 8..850

## (ix) FEATURE:

- (A) NAME/KEY: mat\_peptide
- (B) LOCATION: 427..843

## (ix) FEATURE:

- (A) NAME/KEY: mRNA
- (B) LOCATION: 1..997

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAATTCC GAG CCC CAT TGG AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC  
 Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile  
 -139       -135       -130

CCG GCT GGG GAG GCG GTC ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val	97
-125 -120 -115 -110	
CCC AGC ATC CAC CTG CTC AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG Pro Ser Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln	145
-105 -100 -95	
GTG GTC CAG GAG CAG TCC AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT Val Val Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp	193
-90 -85 -80	
CTT CAG ACG CTC CGA GCT GGA GAC GAG GGC TGG CTG GTG CTG GAT GTC Leu Gln Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val	241
-75 -70 -65	
ACA GCA GCC AGT GAC TGC TGG TTG CTG AAG CGT CAC AAG GAC CTG GGA Thr Ala Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly	289
-60 -55 -50	
CTC CGC CTC TAT GTG GAG ACT GAG GAT GGG CAC AGC GTG GAT CCT GGC Leu Arg Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly	337
-45 -40 -35 -30	
CTG GCC GGC CTG CTG GGT CAA CGG GCC CCA CGC TCC CAA CAG CCT TTC Leu Ala Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe	385
-25 -20 -15	
GTG GTC ACT TTC TTC AGG GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG Val Val Thr Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg	433
-10 -5 1	
GCA GTG AGG CCA CTG AGG AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG Ala Val Arg Pro Leu Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu	481
5 10 15	
CCG CAG GCC AAC CGA CTC CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC Pro Gln Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser	529
20 25 30 35	
CAC GGC CGG CAG GTC TGC CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG His Gly Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln	577
40 45 50	
GAC CTT GGC TGG CTG GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala	625
55 60 65	
TAT TAC TGT GAG GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn	673
70 75 80	

GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG GTG CAC CTG ATG AAG CCA Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro	721
85            90            95	
AAC GCA GTC CCC AAG GCG TGC TGT GCA CCC ACC AAG CTG AGC GCC ACC Asn Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr	769
100            105            110            115	
TCT GTG CTC TAC TAT GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His	817
120            125            130	
CGC AAC ATG GTG GTC AAG GCC TGC GGC TGC CAC TGAGTCAGCC CGCCCAGCCC Arg Asn Met Val Val Lys Ala Cys Gly Cys His	870
135            140	
TACTGCAGCC ACCCTTCTCA TCTGGATCGG GCCCTGCAGA GGCAGAAAAC CCTTAAATGC	930
TGTCACAGCT CAAGCAGGAG TGTCAGGGC CCTCACTCTC GGTGCCTACT TCCTGTCAGG	990
CTTCTGGGAA TTC	1003

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 281 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala  
-139            -135            -130            -125

Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser  
-120            -115            -110

Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val  
-105            -100            -95

Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln  
-90            -85            -80

Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val Thr Ala  
-75            -70            -65            -60

Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly Leu Arg  
-55            -50            -45

Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly Leu Ala  
 -40            -35            -30

Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe Val Val  
 -25            -20            -15

Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg Ala Val  
 -10            -5            1            5

Arg Pro Leu Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln  
 10            15            20

Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly  
 25            30            35

Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu  
 40            45            50

Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr  
 55            60            65

Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr  
 70            75            80            85

Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro Asn Ala  
 90            95            100

Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val  
 105            110            115

Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn  
 120            125            130

Met Val Val Lys Ala Cys Gly Cys His  
 135            140

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 112 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His Glu Leu  
1           5           10           15

Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Leu Leu Val Ile Ala Pro  
20           25           30

Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu  
35           40           45

Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val  
50           55           60

His Leu Leu Lys Pro His Ala Val Pro Lys Ala Cys Cys Ala Pro Thr  
65           70           75           80

Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val  
85           90           95

Ile Leu Arg Lys His Arg Asn Met Val Val Arg Ala Cys Gly Cys His  
100          105          110

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Rod Hewick, et al.

Serial No.: 07/800,364

Examiner: K. Furman

Filed : November 26, 1991

Art Unit: 1814

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 13, 1994

Hon. Commissioner  
 of Patents and Trademarks  
 Washington, D.C. 20231  
 ATTN: Donna Chapman, Supervisor

<u>Certificate of Facsimile Transmission</u>	
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.	
<u>Diana Gentile</u>	Type or print name of person signing certificate.
<u>Diana Gentile</u>	Signature
1/13/94	
Date	

## LETTER

This is in response to the telephone conference with Ms. Donna Chapman January 11, 1994. Ms. Chapman instructed Applicants to send or fax a copy of the amendment filed August 4, 1993. Although this amendment was received by the Patent and Trademark Office as evidenced by the enclosed return postcard bearing an August 4, 1993 mailroom stamp, a Notice of Abandonment was received September 17, 1993.

Ms. Chapman indicated during the January 11 telephone conference that extension and other fees relating to this application had in fact been charged to Applicants' Deposit Account No. 07-1060.

The following documents are faxed herewith to (703) 305-3014.

1. Mail room receipt postcard bearing August 4, 1993 stamp
2. Transmittal Letter (1 page)
3. Extension of Time (1 page)
4. Information Disclosure Statement (2 pages)
5. Form PTO-1449 (2 pages)
6. Amendment with Appendix A (20 pages)
7. Deposit Declaration (2 pages)

A copy of these documents as well as ten references listed on PTO-1449 and PCT/US91/03388 are being hand delivered to Ms. Chapman within a few days.

In view of the above, it is respectfully submitted that the Notice of Abandonment be withdrawn and the response of August 4, 1993 be considered by the Examiner.

No fee is believed due. However, if any fee should be due, authorization is hereby given to charge it to our Deposit Account No. 07-1060. Two copies of this sheet are enclosed.

Respectfully submitted,

January 13, 1994  
Date

Ellen J. Kapinos  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants

Legal Affairs  
GENETICS INSTITUTE, INC.  
87 CambridgePark Drive  
Cambridge, Massachusetts 02140

**PATENT**

Serial No. 07/800,364 Doc. No. 61-5782A Atty/Sec EK/06 Date 1/17/94  
Inventor Rod Henick, et al.

Title Bone and Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

- |  |  |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> Claim, <input type="checkbox"/> Abstract      | X <u>20</u> pp. Amendment/ <sup>1/17/94</sup> OA dtd <u>2-5-93</u> |
| <input type="checkbox"/> pp. Declaration/Power of Attorney   | <input type="checkbox"/> pp. Response: OA dtd _____                |
| <input type="checkbox"/> pp. Verified Statement (Small Entity)   | X <u>1</u> pp. Transmittal Letter <u>(copy)</u>                    |
| <input type="checkbox"/> shts. Informal Drawings   | <input type="checkbox"/> Issue Fee                                 |
| <input type="checkbox"/> shts. Formal Drawings   | <input type="checkbox"/> Notice of Appeal & Fee                    |
| <input type="checkbox"/> pp. Assignment  | <input type="checkbox"/> Check # _____ for \$ _____                |
| <input type="checkbox"/> pp. Preliminary Amendment   | X <u>Letter</u>  |
| X <u>1</u> pp. Extension of Time <u>(copy)</u>   | X <u>Deposit Declaration - copy</u>                                |
| X <u>2</u> pp. Information Disclosure Statement<br><u>(copy)</u><br>with PTO-1499 and <u>16</u> references | X <u>Copy of PCT/US91/03386</u>                                    |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

*Confirmation copy to be  
Hand delivered by Betty Byrd, Inc.*

Respectfully,  
Genetics Institute, Inc.

**PATENT**

Serial No. 07/800,364 Doc. No. 61-5782A Atty/Sec EK/06 Date 1/17/94  
Inventor Rod Henick, et al.

Title Bone and Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

- |  |  |
|--|--|
| <input type="checkbox"/> pp. Spec., <input type="checkbox"/> Claim, <input type="checkbox"/> Abstract      | X <u>20</u> pp. Amendment/ <sup>1/17/94</sup> OA dtd <u>2-5-93</u> |
| <input type="checkbox"/> pp. Declaration/Power of Attorney   | <input type="checkbox"/> pp. Response: OA dtd _____                |
| <input type="checkbox"/> pp. Verified Statement (Small Entity)   | X <u>1</u> pp. Transmittal Letter <u>(copy)</u>                    |
| <input type="checkbox"/> shts. Informal Drawings   | <input type="checkbox"/> Issue Fee                                 |
| <input type="checkbox"/> shts. Formal Drawings   | <input type="checkbox"/> Notice of Appeal & Fee                    |
| <input type="checkbox"/> pp. Assignment  | <input type="checkbox"/> Check # _____ for \$ _____                |
| <input type="checkbox"/> pp. Preliminary Amendment   | X <u>Letter</u>  |
| X <u>1</u> pp. Extension of Time <u>(copy)</u>   | X <u>Deposit Declaration - copy</u>                                |
| X <u>2</u> pp. Information Disclosure Statement<br><u>(copy)</u><br>with PTO-1499 and <u>16</u> references | X <u>Copy of PCT/US91/03386</u>                                    |

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

*Confirmation copy to be  
Hand delivered by Betty Byrd, Inc.*

Respectfully,  
Genetics Institute, Inc.

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS  
WASHINGTON, D.C. 20591

SERIAL NO.: 07/800,364  
FILED: November 26, 1991  
GROUP ART UNIT: 1814

SIR:

In re application of: Rod Hewick et al.

Entitled: BONE AND CARTILAGE INDUCTIVE PROTEINS

Transmitted herewith is an Amendment in the above-identified application. The following checked items are applicable:

- A Petition for Extension of Time for 3 months is hereby made, under §1.136(a) and fee is calculated herein;
- Other: Declaration of Deposit Requirements and enclosures  
Information Disclosure Statement with 10 references attached.

Claims after amendment	Minus Prior PAID claims	Equals present extra claims	RATE	FEE
Independent 8	- 13	=	x \$74.00 =	\$ .00
Total 21	- 25	=	x \$22.00 =	\$ .00
[ ] Multiple Dependent Claims (1st presentation)			+\$230.00	\$ .00
<input checked="" type="checkbox"/> Information Disclosure fee pursuant to revised §1.97 & §1.98			+\$200.00	\$200.00
			SUBTOTAL FEE	\$ .00
<input checked="" type="checkbox"/> Petition for Extension of time fee pursuant to §1.17 extension within 3 months				\$840.00
			TOTAL ADDITIONAL FEE	\$840.00

The fee has been calculated above; The Commissioner is hereby authorized to charge payment of \$840.00 under §1.16 associated with this communication or credit any overpayment to Deposit Account No. 07-1060.

[ ] No additional fee is believed due.

CERTIFICATE OF MAILING RB 793966844 US  
Date of Deposit August 4, 1993

I hereby certify that this correspondence is being deposited with the United States Postal Service Via Express Mail Post Office to "Addressee" service under 37 C.F.R. 1.10 on date indicated above and addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Ellen J. Kapinos  
Attorney of Record: Ellen J. Kapinos  
Registration No. 32,245

SUBMITTED IN TRIPPLICATE

Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick et al.

Serial No. : 07/800,364

Examiner : K. Kurman

Filed : November 26, 1991

Art Unit : 1814

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

RB 793966844 US  
"Express Mail" mailing label number:Date of Deposit: August 4, 1993

August 2, 1993

Hon. Commissioner of  
Patents and Trademarks  
Washington, DC 20231

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231,

*Ellen J. Kapinos*

PETITION AND FEE FOR EXTENSION OF TIME UNDER 37 CFR 1.136

We hereby request an extension of time for response of three (3) month/s pursuant to 37 CFR 1.136(a) in which to respond to the Office Action mailed February 5, 1993. This extension resets the time for response from May 5, 1993 to August 5, 1993.

We authorize the charging of Eight Hundred and Forty (\$840.00) and any additional fees and crediting of overpayment to our Deposit Account 07-1060, and for this purpose, we enclose a duplicate copy of this petition.

Respectfully submitted,

Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
(617)-876-1170

August 3, 1993  
Date

Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140-2387

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick et al.

Serial No. : 07/800,364

Examiner : K. Furman

Filed : November 26, 1991

Art Unit : 1814

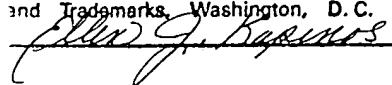
For : BONE AND CARTILAGE INDUCTIVE PROTEINS

August 2, 1993

Hon. Commissioner of  
Patents and Trademarks  
Washington, DC 20231

"Express Mail" mailing label number, R8793966844 US  
Date of Deposit: August 4, 1993

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R.I. 10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.



Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the provisions of 37 C.F.R. §§ 1.56 and 1.97, 1.98(d) the publications and/or patents listed on the attached form PTO-1449 are cited for consideration by the Examiner in connection with the examination of the above-identified patent application. It is understood that the references need not be provided herewith as they have been previously submitted to the Office in the prior parent application. Those references which are marked by an asterisk have been provided herewith as they were not cited in the parent and comprise the most recent relevant art of which applicant is aware.

In accordance with the provisions of 37 C.F.R. §1.97, this statement is being filed (CHECK ONE):

- (1) within three (3) months of the Filing Date or before the mailing date of the First Office Action on the merits; or
- (2) after the period defined in (1) but before the mailing date of a Final Rejection or Notice of Allowance, and the requisite Certification or fee under Rule 1.17(p), namely \$200.00, is included herein; or
- (3) after the mailing date of a Final Rejection or Notice of Allowance but before the payment of the Issue Fee, and the requisite Certification, petition, and petition fee are included herein.

It is respectfully requested that each of the documents shown on the attached form PTO-1449 be made of record in this application.

Early examination and allowance of the present application are respectfully solicited.

Should any fee associated with the submission of this paper not be attached hereto as a check, the Commissioner is authorized to charge the missing fee to our Deposit Account, No. 07-1060. Any overpayments should be credited to said Deposit Account.

Respectfully submitted,



Legal Affairs  
Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, Massachusetts 02140

Ellen J. Kepinos  
Reg. No. 32,245  
Attorney for Applicants  
(617)-876-1170

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Hewick et al

Group Art Unit: 1814

Serial No.: 07/800,364

Examiner : K. Furman

Filed : November 26, 1991

For : DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS

August 4, 1993

Hon. Commissioner of Patents  
and Trademarks  
Washington, DC 20231

RB 793966844 US  
"Express Mail" mailing label number.

Date of Deposit August 4, 1993

I hereby certify that this paper or fee is  
deposited with the United States Postal Service  
"Express Mail Post Office to Addressee" under  
37 C.F.R. 1.10 on the date indicated  
and is addressed to the Commissioner of Patents  
and Trademarks, Washington, D.C. <sup>2</sup>

*Ellen J. Krasin*

Sir:

This is in response to the Office Action mailed February 5, 1993. A Request for a Three Month Extension and Fee accompanies this amendment. The Extension resets the time for response from May 5, to April 5, 1993.

Please amend the application as follows:

In the Specification:

Change the title to -- DNA ENCODING AND METHODS FOR PRODUCING BMP-8 PROTEINS --

Page 1, line 34, delete "Figure 2".

Page 2, insert the numeral --2-- at the top center of the page.

Page 2, lines 2-3, delete "#143 (Ala)- #281 (His) of Figure 2" and insert -- #4 (Ala) - #142 (His) of SEQ ID NO: 14, therefor.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

Page 2, line 4, delete "Figure 2" and insert -- SEQ ID NO: 14-- therefor.

Page 2, line 35, delete "#1 through #843" and insert --#8 through #850--, therefor.

Page 3, line 1 delete "Figure 2".

Page 4, lines 4-5 delete "#143 through #281 of Figure 2" and insert --#4 through #142--, therefor.

Page 4, line 15, delete "#1 to #843 in Figure 2" and insert -- #8 to #850 of SEQ ID NO: 13--, therefor.

Page 4, lines 17 and 22, delete " #143 to #281 of Figure 2" and insert -- #4 to # 142 of SEQ ID NO: 14 -- , therefor.

Page 4, line 23 delete "#143" and insert --#4--, therefor.

Page 6, line 24 delete "Figure 2".

Page 8, line 1, delete "#143 through 281 of Figure 2" and insert -- #4 through #142 of SEQ ID NO: 14 --, therefor.

Page 8, lines 7-8, delete "#143 (Ala) - #281 (His) of Figure 2" and insert --#4 (Ala) - #142 (His) of SEQ ID NO: 14--, therefor.

Page 8, lines 9 and 13, delete "Figure 2" and insert --SEQ ID NO:14 --, therefor.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

Page 11, line 20, delete "#143 through #281 of Figure 2" and insert -- #4 through #142 of SEQ ID NO: 14 --, therefor.

Page 11, line 23, delete "Figure 2" and insert --SEQ ID NO:14--, therefor.

Page 11, lines 27-28, delete "#143 (Ala) - #281 (His) of Figure 2" and insert -- #4 (Ala) - #142 (His) of SEQ ID NO: 14--, therefor.

Page 11, line 29, delete "Figure 2" and insert -- SEQ ID NO: 14--.

Page 29, line 22, delete "fragmnet" and insert --fragment--, therefor.

Page 32, lines 6-7 delete "(SEQ ID NO:13)".

Page 32, line 7, after "Table 4" insert -- which corresponds to the sequence of SEQ ID NO:14 from amino acid position number 31 through position 142, wherein Met at position 97 is replaced with Leu, Asn at position 100 is replaced with His, and Lys at position 137 is replaced with Arg. --

Page 35, line 33, delete "Figure represent" and insert --SEQ ID NO:14 represents--, therefor.

Page 36, line 7, delete "#143 - #281 of Figure 2" and insert -- #4 - #142 of SEQ ID NO: 14--, therefor.

Page 36, line 9, delete "Figure 2" and insert --SEQ ID NO:14--, therefor.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

Page 36, line 11, delete "Figure 2" and insert --SEQ ID NO:13--, therefor.

Page 37, line 32, delete "#1 to #846 of Figure 2" and insert -- #8 to #853 of SEQ ID NO:13--, therefor.

In the Claims:

6. (once amended) An isolated DNA sequence [encoding a BMP-8 protein said DNA sequence] comprising [at least one of] the following sequences

a)

GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC CAC (SEQ ID NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GCC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG  
TGC CGTCGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID NO: 11).

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

[d) the nucleotide sequence comprising nucleotide #1 through #843 of Figure 2 (SEQ ID NO:13); and

e) the nucleotide sequence comprising nucleotide #430 through #843 of Figure 2 (SEQ ID NO:13).]

7. (twice amended) An isolated DNA sequence comprising the nucleotide sequence set forth in [Figure 2 ()SEQ ID NO:13()] from nucleotide #[1]8 to #[843]850.

8. (twice amended) An isolated DNA sequence comprising the nucleotide sequence set forth in [Figure 2 ()SEQ ID NO: 13()] from nucleotide #[430]434 through #[843]850.

9. (once amended) An isolated DNA comprising [T]the DNA sequence of ATCC #75010 [encoding BMP-8].

17. (once amended) A method [for producing a BMP-8 protein said method] comprising the steps of:

(a) culturing a cell transformed with a vector comprising [having] a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

medium a protein encoded by said DNA sequence [characterized by the ability to induce cartilage and/or bone formation].

18. (once amended) A method [for producing a purified BMP-8 protein said method] comprising the steps of

- (a) culturing a cell transformed with a vector comprising [having] a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence [characterized by the ability to induce cartilage and/or bone formation].

19. (twice amended) A method [for producing a purified BMP-8 protein said method] comprising the steps of:

- (a) culturing a cell transformed with a vector comprising [having] a DNA sequence comprising nucleotide #[1]8 through #[843]850 of [Figure 2] SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and
- (b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #[143]4 to #[281]142 of [Figure 2] (SEQ ID NO:14).

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

Add new claims:

26. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

28. A DNA sequence encoding a protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

- b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-  
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and  
  
c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3).

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

33. A method comprising

a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and

b) recovering, isolating and purifying from said culture medium a BMP-8 characterized by the following sequences

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-  
Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:  
1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-  
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

34. A method for isolating a DNA sequence comprising

a) designing nucleotide probes based on the following amino acid sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-  
Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:  
1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-  
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2);

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

b) screening a selected library with said probes; and isolating said DNA sequence from said library said DNA encoding a protein comprising the sequences set forth in i) through iii).

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

35. An isolated DNA sequence comprising the nucleotide sequence of ATCC #75011.

REMARKS

Reconsideration of the application and entry of the amendments is requested.

The following documents accompany this response:

1. Appendix A - Claims
2. Information Disclosure Statement, PTO Form 1449, required fee and references.
3. Petition for Extension of Time and Required Fee
4. Deposit Declaration

The Draftsman's Drawing Review has been noted. In accordance with 37 CFR 1.85, Applicants will submit corrected formal drawings upon notification of allowance of claims in the present application.

Applicants have requested a certified copy of PCT/US91/03388 for which priority is claimed under 35 USC 119. A copy of PCT/US91/03388 is enclosed and the certified copy will be forwarded as soon as it is received.

Minor amendments have been made to the specification. The title has been changed to reflect the nature of the claimed invention. Claims 1-5, 10-12 and 20-25 have been deleted. Claims

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

6-9 and 17-19 have been amended. New claims 26-35 have been added. Basis for the new claims appears throughout the specification for example, claims 26, 27 and 33: page 10, line 30 to page 12, line 29, page 36, line 25 to page 39, line 20; claim 28, page 3, lines 10-22; claims 29 and 30, page 8, lines 28-33; claim 31, page 12, line 30 to page 13, line 10; claim 32, page 10, lines 4-18; claim 34, page 8, line 34 to page 9, line 4 and page 34, line 28 to page 35, line 8; and claim 35, page 28, line 24 to page 35, line 4. For convenience the claims as amended appear in Appendix A.

An Information Disclosure Statement, Form 1449 and authorization to charge the \$200.00 fee to Deposit Account No. 07-1060 accompanies this document. Copies of listed references which have not been previously submitted in parent applications are submitted herewith.

The objections and rejections are addressed below in order of their appearance in the office action.

Restriction Requirement

Applicants hereby confirm the election of Group II, claims 6-9 and 13-19. It is Applicants understanding that an election of species is not necessary because all species were searched and examined on the merits. Claims 1-5, 10-12 and 20-25 stand withdrawn from further consideration in this Application. Applicants hereby preserve their rights to pursue the subject matter contained in these withdrawn claims in one or more divisional applications filed pursuant to 35 U.S.C. 121. It is believed that the inventorship remains the same despite the withdrawal of non-elected claims.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

Rejections Based on 35 USC §112

The specification is objected to as failing to provide an adequate written description of the invention because of an error in referencing a SEQ ID for the bovine BMP-8 sequence in the last line of page 32. The specification has been amended, as suggested by the Examiner, indicating that the bovine BMP-8 sequence of Table 4 "corresponds to the sequence of SEQ ID NO:14 from amino acid position number 31 through position 142 wherein Met at position 97 is replaced with Leu, Asn at position 100 is replaced with His and Lys at position 137 is replaced with Arg."

The written description is also considered inadequate because where a SEQ ID NO: follows a reference to a Figure it is not clear whether the sequence of the SEQ ID is the equivalent of the entire Figure or the range of positions in the Figure because the position numbers in the Figures differ from the numbers in the SEQ ID. The specification has been amended to specifically reference the SEQ ID and position numbers for the SEQ ID. Reference to Figure 2 has been deleted. The specification as amended is considered to provide an adequate written description.

Claims 6, 13 and 17 are rejected as the disclosure is enabling only for claims limited to where the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2. It is submitted that the claims as amended are enabled by the disclosure. Claim 6 as amended and claims 13 and 17 dependent thereon are directed to a DNA comprising three sequences [a), b) and c)] which form part of the nucleotide sequence encoding BMP-8.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

Claims 17 and 18 are rejected as the disclosure is enabling only for claims limited wherein the protein recovered in step (b) is the one encoded by the coding regions of the DNA sequence of step (a) in both claims 17 and 18 and in claim 17 wherein the sequence is either that set forth in d) or e) or DNAs which encode the same protein(s) encoded by the DNAs of species d) or e). The claims have been amended to limit the protein recovered in step (b) to proteins encoded by the coding regions of the DNA of step (a). As discussed above, claim 6 (upon which claim 17 depends) has been amended to set forth three nucleotide sequences [a), b) and c)] which comprise part of the DNA sequence encoding BMP-8. It is therefore submitted that the claims as amended are enabled by the disclosure.

The specification is objected to as failing to provide an enabling disclosure for the claimed invention because the sequence of the DNA encoding BMP-8 of ATCC #75010 is not elsewhere disclosed and this DNA is claimed. The Examiner contends that the specification does not provide a repeatable method for obtaining ATCC #75010. Applicants submit that the description set forth on page 33, line 26 through page 34, line 27 provides a repeatable method for obtaining the DNA encoding BMP-8 of ATCC #75010. As suggested by the Examiner, a Declaration by the undersigned Attorney of record is submitted herewith to satisfy the deposit requirements. The Declaration states that ATCC #75010 and #75011 have been deposited under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public will be irrevocably removed upon the granting of a patent. It is therefore considered that the specification provides an enabling disclosure for claims 9 and 18.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

Claims 6-8, 13-15 and 19 are rejected as being indefinite because it is not clear whether the sequence of the SEQ ID NO: is the equivalent of the entire sequence of the Figure or the equivalent of the sequence corresponding to the range of positions in the Figure. Furthermore, it is noted by the Examiner that the position numbers of the Figures do not correspond with the SEQ ID. As recommended by the Examiner the claims have been amended to refer only to the SEQ ID and positions thereof. Claim 19 has been amended to reference a SEQ ID.

Rejections Based on 35 USC §101

Claims 6, 9, 13 and 16 are rejected for being directed to non-statutory subject matter. It is contended that the DNAs of species a), b) and c) of claim 6 and 9 and the host cells have the same characteristics and utility as that found in nature. The claims as amended are directed to isolated DNA sequences and are therefore considered to be distinguished from that found in nature.

In view of the above, it is submitted that the claims as amended are in condition for allowance. Reconsideration of the rejections and objections is requested.

Respectfully submitted,

Date August 4, 1993

Ellen J. Kapinos  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
Tel: (617) 876-1170

Genetics Institute, Inc.  
87 Cambridge Park Drive  
Cambridge, MA 02140

[legal.patent]5182Aamend

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

APPENDIX A

6. An isolated DNA sequence comprising the following sequences

a)

GTC CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC ACC  
AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC  
CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC CAC (SEQ ID  
NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GCC TAC TCA GCC TAT TAC TGT GAA GGG GAG  
TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG  
CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG  
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID NO:  
11).

7. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO:13 from nucleotide #8 to #850.

8. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO: 13 from nucleotide #434 through #850.

9. An isolated DNA comprising the DNA sequence of ATCC #75010.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

13. A host cell transformed with a DNA of claim 6.

14. A host cell transformed with the DNA of claim 7.

15. A host cell transformed with the DNA of claim 8.

16. A host cell transformed with the DNA of claim 9.

17. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

18. A method comprising the steps of

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 9 in operative association with a n expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

19. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence comprising nucleotide #8 through #850 of SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and
- (b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #4 to #142 of (SEQ ID NO:14).

26. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

28. A DNA sequence encoding a protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);
- b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and
- c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3).

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

33. A method comprising

- a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and
- b) recovering, isolating and purifying from said culture medium a BMP-8 characterized by the following sequences

- i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);
- ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and
- iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

34. A method for isolating a DNA sequence comprising

- a) designing nucleotide probes based on the following amino acid sequences

- i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

USSN 07/800,364  
Group Art Unit 1814  
Filed: November 26, 1991

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-  
Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2);

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

b) screening a selected library with said probes; and isolating said DNA sequence from said library said DNA encoding a protein comprising the sequences set forth in i) through iii).

35. An isolated DNA sequence comprising the nucleotide sequence of ATCC #75011.

GI 5182A  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rod Hewick et al.

Group Art Unit : 1814

Serial No.: 07/800,364

Examiner : K. Furman

Filed : November 26, 1991

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

August 2, 1993

Hon. Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

RB 793966844US

"Express Mail" mailing label number:

Date of Deposit: August 4, 1993

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Ellen J. Kapinos

DECLARATION OF DEPOSIT REQUIREMENTS

I, Ellen J. Kapinos, declare as follows:

1. That I am an attorney of record and Senior Patent Attorney of Genetics Institute, the assignee of the above-identified patent application;
2. That the cultures listed below have been deposited in the permanent culture collection of the American Type Culture Collection, 12031 Parklawn Drive, Rockville, Maryland, and the culture deposits meet the requirements of the Budapest Treaty for the purposes of patent procedure;
3. That said cultures have been accorded the accession numbers 75010 and 75011, prior to the filing date of the above-identified patent application;
4. That said cultures have been deposited under conditions which ensure that access thereto will be available during the pendency of the above-identified patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 AND 35 U.S.C. 122;
5. That upon issuance of a patent on the above-identified patent application Genetics Institute, Inc. will remove any restrictions as to public availability of the culture deposits, and

USSN 07/800,364  
August 2, 1993  
Page 2

will replace the same culture deposits should they become nonviable, during the period that extends thirty years from the date of the deposit, or the period of the enforceable life of the patent, or the period of five years after the last public request for the deposit, whichever period is longest; and

6. That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief and believed to true, and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 10 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Genetics Institute, Inc.

Date: August 3, 1993

By: Ellen J. Kapinos  
Ellen J. Kapinos  
Senior Patent Attorney

**PATENT**

Serial No. 800,111Y Doc. No. 174-9-05 Atty/Sec Ex/INN Date Aug 4, 1993

Inventor David M. Dick, Jack Wang, John Wozney, Tony Colaste

Title Lipase and Collagen Inducting Enzymes

*w/ Appendix A*

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

- pp. Spec.,  Claim,  Abstract  20 pp. Amendment: OA dtd Z-5-93  
 pp. Declaration/Power of Attorney  1 pp. Response: OA dtd  
 pp. Verified Statement (Small Entity)  Transmittal Letter in Duplicate  
 shts. Informal Drawings  Issue Fee  
 shts. Formal Drawings  Notice of Appeal & Fee  
 pp. Assignment  Check # 279 for \$ 1  
 pp. Preliminary Amendment  Deposit Declaration  
 1 pp. Extension of Time induplicate  PCT / US 91 / 03388  
 2 pp. Information Disclosure Statement with PTO-1499 and 10 references 12pp

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

*VIA Express Mail*  
RC 72J 966 884US

Respectfully,  
Genetics Institute, Inc.

**PATENT**

Serial No. 800,111Y Doc. No. 174-9-05 Atty/Sec Ex/INN Date Aug 4, 1993

Inventor David M. Dick, Jack Wang, John Wozney, Tony Colaste

Title Lipase and Collagen Inducting Enzymes

*w/ Appendix A*

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

- pp. Spec.,  Claim,  Abstract  20 pp. Amendment: OA dtd Z-5-93  
 pp. Declaration/Power of Attorney  1 pp. Response: OA dtd  
 pp. Verified Statement (Small Entity)  Transmittal Letter in Duplicate  
 shts. Informal Drawings  Issue Fee  
 shts. Formal Drawings  Notice of Appeal & Fee  
 pp. Assignment  Check # 279 for \$ 1  
 pp. Preliminary Amendment  Deposit Declaration  
 1 pp. Extension of Time induplicate  PCT / US 91 / 03388  
 2 pp. Information Disclosure Statement with PTO-1499 and 10 references 12pp



## UNITED STATES DEPARTMENT OF COMMERCE

Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

(22)

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO/TITLE
07/800,364	11/26/91	HEWICK	R 31878

LEGAL AFFAIRS DEPARTMENT  
GENETICO INSTITUTE INC., ET AL.  
COMMERCIAL MA. O. 100



DATE MAILED:

**NOTICE TO FILE MISSING PARTS OF APPLICATION  
FILING DATE GRANTED**

A filing date has been granted to this application. However, the following parts are missing.

If all missing parts are filed within the period set below, the total amount owed by applicant as a

large entity,  small entity (verified statement filed), is \$ 130.

1.  The statutory basic filing fee is:  missing  insufficient. Applicant as a  large entity  small entity, must submit \$ \_\_\_\_\_ to complete the basic filing fee and MUST ALSO SUBMIT THE SURCHARGE AS INDICATED BELOW.
2.  Additional claim fees of \$ \_\_\_\_\_ as a  large entity  small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due. NO SURCHARGE IS REQUIRED FOR THIS ITEM.
3.  The oath or declaration:
  - is missing.
  - does not cover items omitted at time of execution.An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
4.  The oath or declaration does not identify the application to which it applies. An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
5.  The signature to the oath or declaration is:  missing;  a reproduction;  by a person other than the inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW..
6.  The signature of the following joint inventor(s) is missing from the oath or declaration:

\_\_\_\_\_. An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Receipt Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.

7.  The application was filed in a language other than English. Applicant must file a verified English translation of the application and a fee of \$30.00 under 37 CFR 1.17(k), unless this fee has already been paid. NO SURCHARGE IS REQUIRED FOR THIS ITEM.
8.  A \$50.00 processing fee is required for returned checks. (37 CFR 1.21(m)).
9.  Your filing receipt was mailed in error because check was returned without payment.
10.  Other.

An Application Number and Filing Date have been assigned to this application. The missing parts and fees identified above in items 1 and 3-6 must be timely provided ALONG WITH THE PAYMENT OF A SURCHARGE of \$120.00 for large entities or \$60.00 for small entities who have filed a verified statement claiming such status. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given ONE MONTH FROM THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE of this application, WHICHEVER IS LATER, within which to file all missing parts and pay any fees required above to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

Direct the response to, and any questions about, this notice to ATTENTION: Application Division,  
Special Handling Unit.

*(Signature)* **A copy of this notice MUST be returned with response.**

For: Manager, Application Division  
(703) 557-1243

(17)

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Hewick et al.	)	GROUP ART UNIT: 1814
SERIAL NO.: 07/800,364	)	EXAMINER: K. FURMAN
FILED : 26 November 1991	)	
TITLE : Bone and Cartilage Inductive Proteins )		

BOX SEQUENCE  
 Hon. Commissioner of Patents  
 and Trademarks  
 Washington, DC 20231

November 11, 1992

I hereby certify that this correspondence is being  
 deposited with the United States Postal Service  
 first class mail in an envelope addressed to  
 Commissioner of Patents and Trademarks, Wash-  
 ington, D.C. 20231, on November 12, 1992.

PETITION AND FEE FOR EXTENSION OF TIME UNDER 37 CFR 1.136

We hereby request an extension of time for response of two (2) month/s pursuant to 37 CFR 1.136(a) in which to respond to the Notice to Comply with Requirements for Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. This extension resets the time for response from September 12, 1992 to November 12, 1992.

We authorize the charging of \$360.00 and any additional fees and crediting of overpayment to our Deposit Account 07-1060, and for this purpose, we enclose a duplicate copy of this petition.

Respectfully submitted,

Date: November 12, 1992

Ellen J. Kapinos  
 Ellen J. Kapinos  
 Reg. No. 32,245  
 Attorney for Applicant  
 87 Cambridge Park Drive  
 Cambridge, MA 02140  
 (617) 876-1170

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Hewick, et al  
Application Serial No. : 07/800,364  
Filing Date : 26 November 1991  
For : Bone and Cartilage Inductive Proteins

November 11, 1992

Box Sequence  
Honorable Commissioner of  
Patents and Trademarks  
Washington, DC 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service by first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Nov. 12, 1992.

STATEMENT PURSUANT TO 37 CFR 1.825(a)

Sir:

Pursuant to the attached notice dated August 12, 1992 received from the Patent and Trademark Office that the "Sequence Listing" does not comply with the requirements of §§ 1.821 through 1.825 because Sequence to human BMP-8 in Fig. 2 does not comply with the sequence rules, applicant herewith submits an amended Sequence Listing and Preliminary Amendment.

Please substitute this amended Sequence Listing for the originally-filed Sequence Listing. The Sequence Listing and enclosed diskette contain amendments to SEQ ID NOS 1-12 to correct defects and now contains SEQ ID NOS. 1-14.

In addition, the Application Serial Number and filing date are now available and have been provided in the appropriate location in the Sequence Listing.

These amendments present no substantive changes to the Sequences as originally filed. No new matter has been added.

Respectfully submitted,

Date: Nov. 12, 1992

Ellen J. Kapinos  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicant

87 Cambridge Park Drive  
Cambridge, MA 02140

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Hewick et al ) GROUP ART UNIT: 1814  
SERIAL NO.: 07/800,364 )  
FILED : 26 November 1991 )  
TITLE : BONE AND CARTILAGE )  
INDUCTIVE PROTEINS )

November 11, 1992

Hon. Commissioner of Patents  
and Trademarks  
Washington, DC 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on November 12, 1992

*Ellen J. Furman*

PRELIMINARY AMENDMENT

Sir:

In response to the Notice to Comply with Sequence Requirements mailed August 12 and in accordance with the sequence requirements of 37 CFR 1.821(d) please amend the application as follows:

In the Specification:

Insert --(SEQ ID NO: 14)-- after "Figure 2" on the following pages:

page 1, line 34  
page 4, line 5

Insert --(SEQ ID NO: 13)-- after "Figure 2" on the following pages:

page 3, line 1  
page 6, line 24

Insert --(SEQ ID NOS: 13 and 14)-- after "Figure 2" on the following pages:

page 7, line 15  
page 35, line 30

HEWICK ET AL  
November 11, 1992  
Page - 2 -

In the Claims:

Insert --(SEQ ID NO: 14)-- after "Figure 2" in the following claims:

Claims 1(e), 4, 5, 12, 19, and 25

Insert --(SEQ ID NO: 13)-- after "Figure 2" in the following claims:

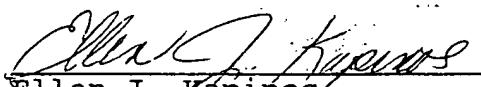
Claims 6 (d) and (e), 7 and 8

REMARKS

Reference to Sequence ID numbers has been made in the specification and claims. The sequences of Figure 2 are depicted (as now referenced in the specification and claims) in SEQ ID NOS: 13 and 14. It is believed that this amendment addresses paragraph 5 of the Notice to Comply. Paragraph 5 indicates that a sequence of the "Listing" is not properly referenced. Though BMP-8 was not originally in the "Listing" it is understood that this is the sequence intended in paragraph 5.

Respectfully submitted,

Date: Nov. 12, 1992

  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicant/s

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Hewick et al ) GROUP ART UNIT: 1814  
SERIAL NO.: 07/800,364 ) EXAMINER: K. Furman  
FILED : 26 November 1991 )  
TITLE : BONE AND CARTILAGE )  
INDUCTIVE PROTEINS )

November 11, 1992

Hon. Commissioner of Patents  
and Trademarks  
Washington, DC 20231

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Commissioner of Patents and Trademarks, Washi-  
ton, D.C. 20231, on Nov. 12, 1992

STATEMENT PURSUANT TO 37 CFR 1.821(f)

Sir:

Pursuant to the duty to submit DNA and amino acid sequence in computer readable form, this affirms that to the best of my knowledge and belief, the content of the SEQUENCE LISTING as provided after the specification and before the claims in the above-identified patent application and the computer readable copy of said SEQUENCE LISTING provided herewith are the same.

Respectfully submitted,

Date: Nov. 12, 1992

Ellen J. Kapinos  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicant

87 CambridgePark Drive  
Cambridge, MA 02140  
(617) 876-1170

## (1) GENERAL INFORMATION:

(i) APPLICANT: Hewick, Rodney M.  
Wang, Jack H.  
Wozney, John M.  
Celeste, Anthony J.

(ii) TITLE OF INVENTION: Bone and Cartilage Inductive Proteins

(iii) NUMBER OF SEQUENCES: 14

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Legal Affairs, Genetics Institute, Inc.  
(B) STREET: 87 CambridgePark Drive  
(C) CITY: Cambridge  
(D) STATE: MA  
(E) COUNTRY: USA  
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/800,364  
(B) FILING DATE: 26-NOV-1991  
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Kapinos, Ellen J.  
(B) REGISTRATION NUMBER: 32,245  
(C) REFERENCE/DOCKET NUMBER: GI 5182A

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617-876-1170  
(B) TELEFAX: 617-876-5851

## (2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(F) TISSUE TYPE: Bone

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp  
 1               5                   10                   15  
 Val Ile Ala Pro Gln Gly Tyr  
 20

## (2) INFORMATION FOR SEQ ID NO:2:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

## (vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile  
 1               5                   10                   15  
 Leu Arg

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

## (vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ala Cys Cys Ala Pro Thr Lys  
 1               5

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

## (vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus
- (F) TISSUE TYPE: Bone

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Thr	Asn	Glu	Leu	Pro	Pro	Pro	Asn	Lys	Leu	Pro	Gly	Ile	Phe	Asp	Asp
1				5						10					15

Val	His	Gly	Ser	His	Gly	Arg
						20

## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 80 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

## (vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus

## (vii) IMMEDIATE SOURCE:

- (B) CLONE: acc30

## (viii) POSITION IN GENOME:

- (C) UNITS: bp

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 25..57

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GGATCCGCGT	GCTGTGCTCC	GACC	AAG	CTG	AGC	GCC	ACC	TCC	GTG	CTC	TAC
Lys	Leu	Ser	Ala	Thr	Ser	Val	Leu	Tyr			
1				5							

TAC GAC AGCAGCAACA ATGTAATTCT AGA  
Tyr Asp  
10

44

80

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 11 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp  
1 5 10

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 199 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:  
(A) ORGANISM: Bos Taurus

(vii) IMMEDIATE SOURCE:  
(A) LIBRARY: Bovine genomic  
(B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:  
(C) UNITS: bp

(ix) FEATURE:  
(A) NAME/KEY: exon  
(B) LOCATION: 30..199

(ix) FEATURE:  
(A) NAME/KEY: intron  
(B) LOCATION: 1..29

(ix) FEATURE:  
(A) NAME/KEY: CDS  
(B) LOCATION: 30..179

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TGCCCGCTGC CCCCTCCCGC CCCCCGCCAG GTG CAC CTG CTG AAG CCG CAC GCG  
Val His Leu Leu Lys Pro His Ala  
1 5

53

GTC CCC AAG GCG TGC TGC GCG CCC ACC AAG CTG AGC GCC ACT TCC GTG	45		
Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val			
10	15	20	
CTC TAC TAC GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC CGC AAC			
Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn			
25	30	35	40
ATG GTG GTC CGC GCC TGC GGC TGC CAC TGAGGCCCA ACTCCACCGG			
Met Val Val Arg Ala Cys Gly Cys His			
45		50	
CAG			
			199

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 49 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Val His Leu Leu Lys Pro His Ala Val Pro Lys Ala Cys Cys Ala Pro			
1	5	10	15
Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn			
20	25	30	
Val Ile Leu Arg Lys His Arg Asn Met Val Val Arg Ala Cys Gly Cys			
35	40	45	
His			

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 172 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: Bos taurus
- (vii) IMMEDIATE SOURCE:
  - (A) LIBRARY: Bovine genomic
  - (B) CLONE: Lambda 9800-10
- (viii) POSITION IN GENOME:
  - (C) UNITS: bp

## (ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 51..161

## (ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..50

## (ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 162..172

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 51..161

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGGGTGGGAG GGCACGTGGA TGGGACTCAC CTTCTCCAC TACCCCCAG GAC TGG	56
Asp Trp	
1	
GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG GAG TGC	
Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys	
10	
15	
TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC ATC CTG	
Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu	
20	
25	
30	
CAG TCC CTG GTCAGTACCT C	
Gln Ser Leu	
35	

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly	
1	
5	
10	
15	
Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala	
20	
25	
30	
Ile Leu Gln Ser Leu	
35	

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 119 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Bos taurus

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Bovine genome
- (B) CLONE: Lambda 9800-10

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION: 20..99

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 1..19

(ix) FEATURE:

- (A) NAME/KEY: intron
- (B) LOCATION: 100..119

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 22..99

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CCCTTGCCTG TCCCCGAGA C GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG	51
Asp Val His Gly Ser His Gly Arg Gln Val	
1 5 10	

TGC CGT CGG CAC GAG CTG TAC GTG AGC TTC CAG GAC CTG GGC TGG CTG	99
Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu	
15 20 25	

GTGAGTTCCG ACTCTCCTTT

119

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

48

Asp	Val	His	Gly	Ser	His	Gly	Arg	Gln	Val	Cys	Arg	Arg	His	Glu	Leu
1				5			10							15	
Tyr	Val	Ser	Phe	Gln	Asp	Leu	Gly	Trp	Leu						
			20				25								

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1003 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
- (F) TISSUE TYPE: Human Heart

(vii) IMMEDIATE SOURCE:

- (A) LIBRARY: Human heart cDNA library stratagene catalog  
#936208
- (B) CLONE: hH38

(viii) POSITION IN GENOME:

- (C) UNITS: bp

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 8..850

(ix) FEATURE:

- (A) NAME/KEY: mat\_peptide
- (B) LOCATION: 427..843

(ix) FEATURE:

- (A) NAME/KEY: mRNA
- (B) LOCATION: 1..997

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAATTCC GAG CCC CAT TGG AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC  
Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile  
-139 -135 -130

49

CCG GCT GGG GAG GCG GTC ACA GCT GCG GAG TTC CCG ATT TAC AAG GTG  
Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val  
-125 -120 -115 -110

97

CCC AGC ATC CAC CTG CTC AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG  
Pro Ser Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln  
-105 -100 -95

145

GTG GTC CAG GAG CAG TCC AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT  
Val Val Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp  
-90 -85 -80

193

CTT CAG ACG CTC CGA GCT GGA GAC GAG GGC TGG CTG GTG CTG GAT GTC Leu Gln Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val -75 -70 -65	241
ACA GCA GCC AGT GAC TGC TGG TTG CTG AAG CGT CAC AAG GAC CTG GGA Thr Ala Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly -60 -55 -50	289
CTC CGC CTC TAT GTG GAG ACT GAG GAT GGG CAC AGC GTG GAT CCT GGC Leu Arg Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly -45 -40 -35 -30	337
CTG GCC GGC CTG CTG GGT CAA CGG GCC CCA CGC TCC CAA CAG CCT TTC Leu Ala Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe -25 -20 -15	385
GTG GTC ACT TTC TTC AGG GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG Val Val Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg -10 -5 1	433
GCA GTG AGG CCA CTG AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG Ala Val Arg Pro Leu Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu 5 10 15	481
CCG CAG GCC AAC CGA CTC CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC Pro Gln Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser 20 25 30 35	529
CAC GGC CGG CAG GTC TGC CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG His Gly Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln 40 45 50	577
GAC CTT GGC TGG CTG GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala 55 60 65	625
TAT TAC TGT GAG GGG GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn 70 75 80	673
GCC ACC AAC CAC GCC ATC CTG CAG TCC CTG GTG CAC CTG ATG AAG CCA Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro 85 90 95	721
AAC GCA GTC CCC AAG GCG TGC TGT GCA CCC ACC AAG CTG AGC GCC ACC Asn Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr 100 105 110 115	769
TCT GTG CTC TAC TAT GAC AGC AGC AAC AAC GTC ATC CTG CGC AAG CAC Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His 120 125 130	817
CGC AAC ATG GTG GTC AAG GCC TGC GGC TGC CAC TGAGTCAGCC CGCCCAGCCC Arg Asn Met Val Val Lys Ala Cys Gly Cys His 135 140	870
TACTGCAGCC ACCCTTCTCA TCTGGATCGG GCCCTGCAGA GGCAGAAAAC CCTTAAATGC TGTACAGCT CAAGCAGGAG TGTCAGGGGC CCTCACTCTC GGTGCCTACT TCCTGTCAGG	930
	990

CTTCTGGGAA TTC

1003

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 281 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Glu Pro His Trp Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala  
 -139                    -135                    -130                    -125

Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser  
 -120                    -115                    -110

Ile His Leu Leu Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val  
 -105                    -100                    -95

Gln Glu Gln Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln  
 -90                    -85                    -80

Thr Leu Arg Ala Gly Asp Glu Gly Trp Leu Val Leu Asp Val Thr Ala  
 -75                    -70                    -65                    -60

Ala Ser Asp Cys Trp Leu Leu Lys Arg His Lys Asp Leu Gly Leu Arg  
 -55                    -50                    -45

Leu Tyr Val Glu Thr Glu Asp Gly His Ser Val Asp Pro Gly Leu Ala  
 -40                    -35                    -30

Gly Leu Leu Gly Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe Val Val  
 -25                    -20                    -15

Thr Phe Phe Arg Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg Ala Val  
 -10                    -5                    1                    5

Arg Pro Leu Arg Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln  
 10                    15                    20

Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly  
 25                    30                    35

Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu  
 40                    45                    50

Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr  
 55                    60                    65

Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr  
 70                    75                    80                    85

Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro Asn Ala  
 90                    95                    100

Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val  
105 110 115

Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn  
120 125 130

Met Val Val Lys Ala Cys Gly Cys His  
135 140

**PATENT**Serial No. 800,364 Doc. No. 5182A Atty/Sec. EK/AIN Date NOV. 12, 1992Inventor RON HENICK ET AL.Title Bone and Cartilage Endocrine Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

- pp. Spec.,  Claim,  Abstract       pp. Amendment: OA dtd 8/12/92  
 pp. Declaration/Power of Attorney       pp. Response: OA dtd \_\_\_\_\_  
 pp. Verified Statement (Small Entity)       pp. Transmittal Letter  
 shts. Informal Drawings       Issue Fee  
 shts. Formal Drawings       Notice of Appeal & Fee  
 pp. Assignment       Check # \_\_\_\_\_ for \$ \_\_\_\_\_  
 pp. Preliminary Amendment       Statement Pursuant to 37 CFR 1.82(a)  
 I pp. Extension of Time & Fee       Sequence Listing pp 41 - 51  
 pp. Information Disclosure Statement       Copy of Notice to Comply to  
with PTO-1499 and \_\_\_\_\_ references       Sequence Disclosure  
 Statement Pursuant to 37 CFR

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Respectfully,  
Genetics Institute, Inc.

1-821(F)

**PATENT**Serial No. 800,364 Doc. No. 5182A Atty/Sec. EK/AIN Date NOV. 12, 1992Inventor RON HENICK ET AL.Title Bone and Cartilage Endocrine Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

- pp. Spec.,  Claim,  Abstract       pp. Amendment: OA dtd 8/12/92  
 pp. Declaration/Power of Attorney       pp. Response: OA dtd \_\_\_\_\_  
 pp. Verified Statement (Small Entity)       pp. Transmittal Letter  
 shts. Informal Drawings       Issue Fee  
 shts. Formal Drawings       Notice of Appeal & Fee  
 pp. Assignment       Check # \_\_\_\_\_ for \$ \_\_\_\_\_  
 pp. Preliminary Amendment       Statement Pursuant to 37 CFR 1.82(a)  
 I pp. Extension of Time & Fee       Sequence Listing pp 41 - 51  
 pp. Information Disclosure Statement       Copy of Notice to Comply to  
with PTO-1499 and \_\_\_\_\_ references       Sequence Disclosure  
 Statement Pursuant to 37 CFR

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Respectfully,  
Genetics Institute, Inc.

1-821(F)



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

(16)

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/800, 364	11/26/91	HEWICK	R 5182A

EXAMINER

FURMAN, K

LEGAL AFFAIRS DEPT.  
GENETICS INSTITUTE, INC.  
87 CAMBRIDGE PARK DR.  
CAMBRIDGE, MA 02140

CONFIRMATION NO.	DATE	ART UNIT	PAPER NUMBER
5182A	5/5/93	1814	10

5/5/93

1814

10

DATE MAILED:

02/05/93

5/5/93

This is a communication from the examiner in charge of your application  
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined  Responsive to communication filed on 1-14-93  This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1.  Notice of References Cited by Examiner, PTO-892.
2.  Notice re Patent Drawing, PTO-948.
3.  Notice of Art Cited by Applicant, PTO-1449.
4.  Notice of Informal Patent Application, Form PTO-152.
5.  Information on How to Effect Drawing Changes, PTO-1474.
6.

**Part II SUMMARY OF ACTION**

1.  Claims 1-25 are pending in the application.

Of the above, claims 1-5, 10-12 and 20-25 are withdrawn from consideration.

2.  Claims \_\_\_\_\_ have been cancelled.

3.  Claims \_\_\_\_\_ are allowed.

4.  Claims 6-9 and 13-19 are rejected.

5.  Claims \_\_\_\_\_ are objected to.

6.  Claims \_\_\_\_\_ are subject to restriction or election requirement.

7.  This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8.  Formal drawings are required in response to this Office action.

9.  The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are  acceptable.  not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10.  The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_ has (have) been  approved by the examiner.  disapproved by the examiner (see explanation).

11.  The proposed drawing correction, filed on \_\_\_\_\_, has been  approved.  disapproved (see explanation).

12.  Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has  been received  not been received  
 been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_

13.  Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14.  Other

**EXAMINER'S ACTION**

Serial No. 07/800,364  
Art Unit 1814

15. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

5 I. Claims 1-5, 10-12 and 20-25, drawn to BMP-8 proteins, pharmaceuticals and methods of treatment, classified in Class 514, subclass 12; and Class 530, subclass 350.

10 II. Claims 6-9 and 13-19, drawn to DNAs, host cells and methods of producing recombinant BMP-8, classified in Class 536, subclass 27; Class 435, subclass 240.2+, depending upon the nature of the cell, and subclass 69.1.

15 16. The inventions are distinct, each from the other because of the following reasons:

The inventions of Group II and Group I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the protein can be made by purification from natural sources using convention purification techniques or combinations of purification techniques including, ion exchange chromatography, hydrophobic interaction chromatography, thiophilic adsorption chromatography, immunoaffinity purification techniques, ultrafiltration, density gradient ultracentrifugation, reverse-phase HPLC and/or other conventional purification techniques. Additionally, the DNA and products containing the DNA of Group II are chemically distinct compounds having separate status in the art as show by their diverse classification and the DNA and host cells can be used other than to make the protein, such as to make additional DNA for use as a probe to detect and/or obtain the same or similar nucleic acid molecules.

17. If Group I is elected, Claims 1, 2, 10 and 20-24 are generic to a plurality of disclosed patentably distinct species comprising (1) species a) of claim 1; (2) species b) of claim 1; (3) species c) of claim 1; (4) species

Serial No. 07/800,364  
Art Unit 1814

d) of claim 1; (5) species e) of claim 1 (i.e. the mature protein also in claims 4, 12 and 25); (6) the species of claim 5, i.e. the intact protein plus presequence) and (7) the human BMP of ATCC #75010 (claims 3 and 11). These species are distinct one from the other because they are drawn to different 5 amino acid sequences required and/or proteins of different size which include portions of sequence not included in the other species which requires searching not required for the other species and therefore requires a separate field of search though they may be classified together. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this 10 requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the 15 examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

18. If Group II is elected, Claims 6, 13 and 17 are generic to a plurality 20 of disclosed patentably distinct species comprising (1) species a) of claim 6; (2) species b) of claim 6; (3) species c) of claim 6; (4) species d) of claim 6 encoding the intact protein plus presequence (also in claims 7, 14 and 19); (5) species e) of claim 6 (i.e. encoding the mature protein also in claims 8 and 15); (6) the DNA of ATCC #75010 including introns (claims 9, 16 and 18). 25 These species are distinct one from the other because they are drawn to different DNA sequences required and/or DNAs of different size which include portions of sequence not included in the other species which requires searching not required for the other species. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement 30 is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

Serial No. 07/800,364  
Art Unit 1814

examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

- 5       19. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and because the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.
- 10      20. During a telephone conversation with Ellen Kapinos on 1-15-93 a provisional election was made with traverse to prosecute the invention of Group II, claim 6-9 and 13-19 and the species of (4) above which reads upon 6, 7, 14 and 19. However, since no prior art was found for the elected species, all the species were searched and examined on the merits in Group II.
- 15      Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-5, 10-12 and 20-25 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.
- 20      21. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.
- 25      22. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).
- 30      23. The following is a quotation of the first paragraph of 35 U.S.C. § 112:  
The specification shall contain a written description of the invention,

and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention. The written description is inadequate because the amino acid sequence of bovine BMP-8 is stated in the last line of p. 32 as corresponding to that of SEQ ID NO: 13. However, this is incorrect for two reasons: (1) SEQ ID NO:13 is a nucleic acid sequence (even though the amino acid sequence is shown); and (2) both SEQ ID NO:13 and SEQ ID NO: 14 correspond to the human BMP-8 nucleic acid and amino acid sequences, respectively, not the bovine amino acid sequence shown in Table 4. Since none of the SEQ ID numbers of the specification correspond to the bovine BMP-8 amino acid sequence of Table 4 and since the bovine amino acid sequence differs from the human sequence at only three amino acid positions, it is suggested that the specification refer to the bovine BMP-8 amino acid sequence of Table 4 as corresponding to the sequence of SEQ ID NO: 14 from amino acid position number 31 through position 142 wherein Met at position 97 is replaced with Leu, Asn at position 100 is replaced with His and Lys at position 137 is replaced with Arg.

The written description is also inadequate because numerous other references to SEQ ID numbers are confusing. At numerous places in the specification particular amino acid or nucleic acid position numbers of a Figure are referred and a particular SEQ ID NO: in parenthesis immediately follows the reference to the Figure but it is not clear whether the sequence of the SEQ ID NO: is the equivalent of the entire sequence of the Figure or the equivalent of the sequence corresponding to the range of positions in the Figure. For example, see line 34 of p. 2 (which is not numbered as page 2) through line 1 of p. 3 and lines 4 and 5 of p. 4. Additionally, the position numbers of the Figure do not correspond to the numbers of the SEQ ID NO:.

Therefore, if applicant refers to both the Figure or Table and the SEQ ID NO: the positions should be specifically noted for each where the sequence is less than the full sequence of the SEQ ID NO.

- 5        25. Claims 6, 13 and 17 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to where the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2. See M.P.E.P.  
10        §§ 706.03(n) and 706.03(z). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The scope of the claims is not reasonably correlated with the scope of enablement of the instant specification because the claims are directed to DNAs which encode a BMP-8 protein, which proteins are defined in the specification as having the ability to stimulate, promote or otherwise induce bone and/or cartilage formation (see p. 3, lines 2-4 and line 24 of p. 4 through p. 6 of the specification), but are limited to merely comprising one of sequences a), b) or c) of the Markush grouping of claim 6. The DNAs of species a), b) and c) of claim 6 have not been shown to encode by themselves (i.e., absent the other coding regions of that set forth in sequence e) of claim 6), to encode a BMP-8 protein having the activities described and would not be expected, by themselves, to encode peptides having this activity since they lack substantial portions of the mature protein. The DNAs comprising at least one of species a), b) and c) are not limited to encoding a protein of particular size which occurs naturally in the source it was obtained from and are open to include any possible addition DNA sequence at either end.  
15        However, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge  
20  
25  
30

of the ways in which the proteins' structure relates to its function. However, the knowledge that may be gleaned from the known members of the BMP family of proteins is limited and precise regions critical to activity do not appear to have been known. Further, it would clearly require undue experimentation to determine the extremely broad scope encompassed by the claims of other non-homologous amino acid sequences which nevertheless have sufficient tertiary structure similarity or other structural similarities sufficient to impart BMP-8 activity to use for the parts of the BMP-8 protein which are not encoded by each of species a), b) or c).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications representative of the essentially infinite the scope broadly set forth is unpredictable based on the instant disclosure and the prior art. Further, one skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Additionally, the specification fails to provide guidance with regard to (A) the general tolerance to modification and extent of such tolerance; (B) specific positions and regions of the sequence(s) which can be predictably modified; (C) which regions are critical to activity; (D) what fragments, if any, can be made which retain the biological activity of the intact protein; and (E) the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546

Serial No. 07/800,364  
Art Unit 1814

(Bd. Pat. App. & Int. 1986).

In addition to the scope set forth above by the Examiner as being reasonably correlated with the enablement of the specification, some additional or other modifications which could be made and used with a reasonable expectation of success, or which would otherwise not require undue experimentation, would also be obvious (e.g. DNAs encoding BMP-8 proteins with minor conservative amino acid substitutions). The specification, however, does not appear to provide antecedent basis for the language of limitations which would encompass all such obvious modifications either because such obvious modifications are not specifically defined or classed in the instant specification, or because it cannot be readily determined or succinctly stated which modifications are so obvious. Therefore, it is expressly noted for the record by the Examiner that limiting the scope of the claims so as to be included within the scope set forth above by the Examiner as enabled should not preclude applicant(s) from protecting under the doctrine of equivalents such additional or other modifications which would also be obvious.

26. Claims 17 and 18 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited wherein the protein recovered in step (b) is the one encoded by the coding regions of the DNA sequence of in step (a) in both claims 17 and 18, and in claims 17 wherein the sequence is either that set forth in d) or e) or DNAs which encode the same protein(s) encoded by the DNAs of species d) of e). See M.P.E.P. §§ 706.03(n) and 706.03(z). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). However, the instant claim does not bear a reasonable correlation with the scope of the enablement because step (b) broadly includes the recovery of any protein having the functional limitations of the ability to induce cartilage and/or bone formation which may be in addition to or even instead of the protein produced by the DNA set forth in step (a). However, applicants have not enabled the extremely broad scope representative of all proteins having

Serial No. 07/800,364  
Art Unit 1814

this function which may even include many other proteins structurally unrelated to the BMP family of proteins nor representative of all possible modifications of the proteins of the BMP family since the amino acid sequence of a given protein determines its structure/function and the sequence

5 information contained in the sequences of the proteins of the BMP family is limited and because it is not routine in the art to screen for multiple substitutions (i.e. beyond that which can be reasonably deduced from differences between homologous proteins having the same structure) to obtain functionally equivalent molecules. Thus, undue experimentation would be  
10 required to support the broad scope of step (b) of the claim. Claim 17 should be limited to the DNA of species d) or e) of as set forth in claim 6 or DNAs which encode the same protein(s) encoded by the DNAs of species d). of e) for the reasons discussed above in the immediately preceding rejection under 35 U.S.C. § 112, first paragraph, regarding the scope of claims 6, 13 and 17.

15 27. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the claimed invention. It is apparent that ATCC #75010 set forth in claim 9 and referred to on p. 34 of the instant specification is required to practice the claimed invention because  
20 the precise sequence of the DNA encoding BMP-8 of ATCC #75010 is not elsewhere disclosed and this DNA is specifically claimed in claims 9 and 18. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. §  
25 112, first paragraph, may be satisfied by a deposit of ATCC #75010. See 37 C.F.R. 1.802.

The specification does not provide a repeatable method for obtaining ATCC #75010 and it does not appear to be readily available material. Deposit of ATCC #75010 would satisfy the enablement requirements of 35 U.S.C. § 112.  
30 If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who

Serial No. 07/800,364  
Art Unit 1814

is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty (as already set forth on p. 34 of the instant specification) and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements.

5 See 37 C.F.R. 1.808.

28. Claims 9 and 18 are rejected under 35 U.S.C. § 112, first paragraph, for 10 the reasons set forth in the objection to the specification.

29. Claims 6-8, 13-15 and 19 are rejected under 35 U.S.C. § 112, second 15 paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6-8 and 19 are indefinite because particular amino acid or nucleic acid position numbers of a Figure are referred and a particular SEQ ID NO: in parenthesis immediately follows the reference to the Figure but it is not 20 clear whether the sequence of the SEQ ID NO: is the equivalent of the entire sequence of the Figure or the equivalent of the sequence corresponding to the range of positions in the Figure. See species d) and e) of claim 6 and claims 6-8. Additionally, the position numbers of the Figure do not correspond to the numbers of the SEQ ID NO:. Therefore, if applicant refers to both the 25 Figure or Table and the SEQ ID NO: the positions should be specifically noted for each where the sequence is less than the full sequence of the SEQ ID NO. However, to avoid redundancy it is suggested that the claims refer only to the SEQ ID NO: and any specific positions thereof rather than to the Figures.

30. Claim 19 is objected to because step (a) contains no reference to a SEQ 30 ID NO: which is required (see 37 CFR § 1.821(d)).

Serial No. 07/800,364  
Art Unit 1814

31. 35 U.S.C. § 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

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32. Claims 6, 9, 13 and 16 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The DNAs of species a), b) and c) of claim 6 and of claim 9 and the host cells, as claimed, has the same characteristics and utility as that found in nature. To overcome this rejection the Examiner suggests the amendment of the claims to include purity limitations which would distinguish the characteristics and utility of applicant's DNA as enabled in the specification from the utility of the DNA it exists in nature. The DNAs of claims 6 and 9 are not limited to having been isolated and the open-ended term "comprising" in claim 6 leaves the claim open to include the other naturally occurring sequence and ingredients associated with these DNAs. The species of claim 9 includes the naturally occurring introns and is not limited to having been isolated. With respect to the host cells of claims 13 and 16, regardless of whether the claims are amended to wherein the DNA is isolated, a host cell merely limited to being transformed with such isolated DNA, would still encompass the natural cells containing the genes since product-by-process limitations would not distinguish over the same products occurring naturally. It is noted that the other products of the claims are not included in the instant rejection because the DNAs are limited with respect to purity and/or inherently exclude naturally occurring intron regions. For relevant case law see Farbenfabriken of Elberfeld Co. v. Kuehmsted, 171 Fed. 887, 890 (N.D. Ill. 1909) (text of claim at 889); Parke-Davis & Co. v. H.D. Mulford Co., 189 Fed. 95, 103, 106, 30 965 (S.D.N.Y. 1911) (claim 1); and In re Bergstrom, 427 F.2d 1394, 1398, 1401-1402 (CCPA 1970).

Serial No. 07/800,364  
Art Unit 1814

33. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The reference of Oppermann et al discloses similar osteogenic proteins and some DNA sequences thereof with their amino acid sequences aligned along with other homologous proteins having somewhat different function/utility (see Figure 18).

5  
34. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit  
10 1814.

15  
35. Papers relating to this application may be submitted to Group 1810 by facsimile transmission. Papers should be faxed to Group 1810 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

20  
36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

25  
January 28, 1993

*Keith C. Furman*  
KEITH C. FURMAN, Ph.D.  
PATENT EXAMINER  
ART UNIT 1814

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602 366

GROUP 18/11

## NOTICE OF DRAFTSMAN'S PATENT DRAWING REVIEW

The PTO Draftsmen review all originally filed drawings regardless of whether they were designated as informal or formal.

The drawings filed 11/16/92

- A.  are approved.  
B.  are objected to under 37 CFR 1.84 for reason(s) checked below. The examiner will require submission of new, corrected drawings at the appropriate time. Corrected drawings must be submitted according to the instructions listed on the back of this Notice.

1. Paper and Ink. 37 CFR 1.84(a)

- Poor Quality Paper. Must Be White.  
Transparent Paper Not Allowed.  
Sheet(s) \_\_\_\_\_

5. Hatching and Shading. 37 CFR 1.84(d)

- Shade Lines are Required.  
Fig(s) \_\_\_\_\_

- Criss-Cross Hatching Not Allowed.  
Fig(s) \_\_\_\_\_

- Double Line Hatching Not Allowed.  
Fig(s) \_\_\_\_\_

- Parts in Section Must be Hatched Properly. Fig(s) \_\_\_\_\_

6. Reference Characters. 37 CFR 1.84(f)

- Reference Characters Poor or Rough and Blurred. Fig(s) \_\_\_\_\_

- Minimum 1/8 inch (3.2 mm.) in height is required. Fig(s) \_\_\_\_\_

- Figure Legends Poor or Placed Incorrectly. Fig(s) \_\_\_\_\_

7. Views. 37 CFR 1.84(i) & (j)

- Figures Must be Numbered Separately.

- Figures Must Not be Connected Fig(s) \_\_\_\_\_

8. Identification of Drawings. 37 CFR 1.84(l)

- Extraneous Matter or Copy Machine Marks Not Allowed. Fig(s) \_\_\_\_\_

9.  Changes Not Completed from Prior PTO-948 dated \_\_\_\_\_

- Proper Size Paper Required. All Sheets Must be Same Size.  
Sheet(s) \_\_\_\_\_

- Proper Margins Required.  
Sheet(s) \_\_\_\_\_  
 Top       Right  
 Left      Bottom

3. Character of Lines. 37 CFR 1.84(c)  
 Lines Pale, Rough and Blurred, or Jagged. Fig(s) \_\_\_\_\_

- Solid Black Shading Not Allowed.  
Fig(s) \_\_\_\_\_

4.  Photographs Not Approved.

Comments:

Telephone inquiries concerning this review should be directed to the Chief Draftsman at telephone number (703) 557-6404.

2/20/92

Reviewing Draftsman

Date

## FILING RECEIPT



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
ASSISTANT SECRETARY AND COMMISSIONER  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

20

SERIAL NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
07/800,364	11/26/91	1806	\$1,460.00	5182A	3	25	13

LEGAL AFFAIRS DEPT.  
GENETICS INSTITUTE, INC.  
87 CAMBRIDGE PARK DR.  
CAMBRIDGE, MA 02140

GN

RECEIVED 5/15/92
DOCKETED TO EK
BY AIN

Receipt is acknowledged of the patent application identified herein. It will be considered in its order and you will be notified as to the examination thereof. Be sure to give the U.S. SERIAL NUMBER, DATE OF FILING, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this transmittal.

Applicant(s) RODNEY M. HEWICK, LEXINGTON, MA; JACK H. WANG,  
LEXINGTON, MA; JOHN M. WOZNEY, HUDSON, MA; ANTHONY J.  
CELESTE, HUDSON, MA.

CONTINUING DATA AS CLAIMED BY APPLICANT-  
THIS APPLN IS A CIP OF 07/525,357 05/16/90  
AND A CIP OF 07/641,204 01/15/91

FOREIGN/PCT APPLICATIONS-PCT

PCT/US91/03388 05/15/91

FOREIGN FILING LICENSE GRANTED 02/19/92  
TITLE  
BONE AND CARTILAGE INDUCTIVE PROTEINS

PRELIMINARY CLASS: 514

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rodney M. Hewick et al

Serial No.: 07/800,364

Filed : November 26, 1991

For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 24, 1992

Hon. Commissioner of Patents  
and Trademarks  
Washington, DC 20231

RESPONSE TO NOTICE TO FILE MISSING PARTS  
OF APPLICATION UNDER 37 C.F.R. 1.53(d)

Sir:

In response to a Notice to File Missing Parts of Application under 37 C.F.R. Section 1.53(d) issued in connection with the above-identified application on January 6, 1992, Applicants hereby submit their Declaration and Power of Attorney pursuant to 37 C.F.R. Section 1.63.

The Declaration refers to the application's above-identified serial number and filing date. As indicated in the Notice, the deadline for submitting the Declaration is February 6, 1992.

Authorization is hereby given to charge the \$120 (One-hundred twenty dollar) surcharge under 37 C.F.R. Section 1.16(e) and any additional fees which may be required in this regard, and to credit any overpayment to Deposit Account No. 07-1060. Two duplicate copies of this letter are enclosed.

Respectfully submitted,

*Ellen J. Kapinos*  
Ellen J. Kapinos  
Registration No. 32,245  
Genetics Institute, Inc.  
87 CambridgePark Drive  
Cambridge, MA 02140-2387  
Phone (617) 876-1170  
Fax (617) 876-5851

I hereby certify that this correspondence is being deposited with the United States Postal Service in first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992.

*Ellen J. Kapinos*

I hereby certify that this correspondence is being  
mailed with the United States Postal Service as  
first class mail in an envelope addressed to Com-  
missioner of Patents and Trademarks, Washing-  
ton, D.C. 20231, on July 24, 1992

Docket No. GI 5182

See my briefs  
**Declaration and Power of Attorney**

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am ~~the original, first and sole inventor (if only one name is listed below) or~~ an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

BONE AND CARTILAGE INDUCTIVE PROTEINS

the specification of which: \_\_\_\_\_ is attached hereto.

X was filed on 11/26/91 as

Application Serial No. 07/800,364

and was amended on \_\_\_\_\_.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information of which I am aware which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, section 119 of any foreign applications(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

<u>Number</u>	<u>Country</u>	<u>Day/Month/Year Filed</u>	<u>Priority Claimed Yes/No</u>
PCT/US91/03388	designated:	15 May 1991	Yes

I hereby claim the benefit under Title 35, United States Code, section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
07/525,357	16 May 1990	Pending
07/641,204	15 January 1991	Pending

\*Austria, Belgium, Switzerland and Liechtenstein, Germany, France, United Kingdom, Italy, Luxembourg, Netherlands, Sweden, Denmark, Spain, Greece, Japan, and Canada

I hereby appoint the following attorneys to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith, to file any International Applications which are based thereon under the provisions of the Patent Cooperation Treaty and to act on my behalf before the competent International Authorities: Bruce M. Eisen, Reg. No. 22,847; Thomas J. DesRosier, Reg. No. 30,168; Luann Cserr, Reg. No. 31,822; Ellen J. Kapnos, Reg. No. 32,245; and Patricia McDaniels, Reg. No. 33,194.

Address all correspondence to Legal Affairs Department, Genetics Institute, Inc., 87 Cambridge Park Drive, Cambridge, MA 02140. Telephone number: 617-876-1170.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Rodney M. Hewick

Inventor's signature R. M. Hewick

Citizenship GB Date: 1/24/92 Residence: 16 Woodcliffe Road  
Lexington, MA 02173  
USA

Post Office address (if different) \_\_\_\_\_

Full name of second joint inventor: Jack H. Wang

Inventor's signature J. H. Wang

Citizenship US Date: 1/24/92 Residence: 522 Lowell Street  
Lexington, MA 02173  
USA

Post Office address (if different) \_\_\_\_\_

Full name of third joint inventor: John M. Wozney

Inventor's signature J. M. Wozney

Citizenship US Date: 1/24/92 Residence: 59 Old Bolton Road  
Hudson, MA 01749  
USA

Post office address (if different) \_\_\_\_\_

Full name of fourth joint inventor Anthony J. Celeste

Inventor's signature Anthony J. Celeste

Citizenship US Date 1/24/92

Residence 86 Packard St., Hudson, MA 01749 USA

Post Office Address (if different) \_\_\_\_\_

Full name of fifth joint inventor \_\_\_\_\_

Inventor's signature \_\_\_\_\_

Citizenship \_\_\_\_\_ Date \_\_\_\_\_

Residence \_\_\_\_\_

Post Office Address (if different) \_\_\_\_\_

Full name of sixth joint inventor \_\_\_\_\_

Inventor's signature \_\_\_\_\_

Citizenship \_\_\_\_\_ Date \_\_\_\_\_

Residence \_\_\_\_\_

Post Office Address (if different) \_\_\_\_\_

**PATENT**

Serial No. 07/800,364 Doc. No. 5182A Atty/Sec ER/EZ Date 1/24/92  
Inventor Rudney M. Hewick et al  
Title Bone + Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon.

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dtd \_\_\_\_\_

id \_\_\_\_\_

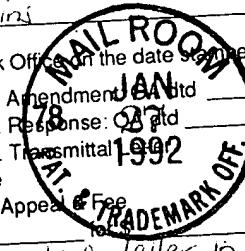
**PATENT**

Serial No. 07/800,364 Doc. No. 5182A Atty/Sec ER/EZ Date 1/24/92  
Inventor Rudney M. Hewick et al  
Title Bone + Cartilage Inductive Proteins

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon.

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|--|---|--|
| <input checked="" type="checkbox"/> <u>3</u> | pp. Spec., <u>1</u> Claim, <u>1</u> Abstract                                  | <input type="checkbox"/> pp. Amendment <u>1</u> dtd <u>1/24/92</u>             |
| <input type="checkbox"/>                     | pp. Declaration/Power of Attorney   | <input type="checkbox"/> pp. Response: OA add <u>1/24/92</u>                   |
| <input type="checkbox"/>                     | pp. Verified Statement (Small Entity)   | <input type="checkbox"/> pp. Transmittal <u>1/24/92</u>                        |
| <input type="checkbox"/>                     | shts. Informal Drawings   | <input type="checkbox"/> Issue Fee <u>1/24/92</u>                              |
| <input type="checkbox"/>                     | shts. Formal Drawings   | <input type="checkbox"/> Notice of Appeal & Fee <u>1/24/92</u>                 |
| <input type="checkbox"/>                     | pp. Assignment  | <input type="checkbox"/> Check # <u>1/24/92</u>                                |
| <input type="checkbox"/>                     | pp. Preliminary Amendment   | <input checked="" type="checkbox"/> Transmitted Letter in <u>Impacted</u>      |
| <input type="checkbox"/>                     | pp. Extension of Time   | <input checked="" type="checkbox"/> Copy of Notice to the Missing <u>Parts</u> |
| <input type="checkbox"/>                     | pp. Information Disclosure Statement<br>with PTO-1499 and <u>1</u> references |  |



The Patent and Trademark Office is respectfully requested to place its stamp on this postal card and place it in the outgoing mail.

Respectfully,  
Genetics Institute, Inc.

Sent via First Class mail

B  
19-

GI 5182A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rodney M. Hewick et al  
Serial No.: 07/800,364  
Filed : November 26, 1991  
For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 24, 1992

Hon. Commissioner of Patents  
and Trademarks  
Box Assignment  
Washington, DC 20231

RECEIVED  
ASSISTANT DIRECTOR

REG-4 M10-21

LETTER

SIR:

Enclosed is an assignment of the above-identified application, executed January 24, 1992, to Genetics Institute, Inc., a corporation of Delaware.

Authorization is hereby given to charge the \$8.00 recordation fee and any additional fees which may be required in this regard, and to credit any overpayment, to Deposit Account No. 07-1060. Two duplicate copies of this letter are enclosed.

Respectfully submitted,

*Ellen J. Kapinos*  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
(617) 876-1170

116294-23

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992.

*Ellen J. Kapinos*

MEL 5988 FILED 7/17

US14256 02/27/92 07800364

07-1060 140 581

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UNITED STATES DEPARTMENT OF COMMERCE

Patent and Trademark Office

ASSISTANT SECRETARY AND COMMISSIONER  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

5182A

DATE: 02/25/92

TO:

ELLEN J. KAPINOS  
GENETICS INSTITUTE, INC.  
87 CAMBRIDGE PARK DRIVE  
CAMBRIDGE, MA 02140

UNITED STATES PATENT AND TRADEMARK OFFICE  
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS, ON THIS NOTICE, PLEASE SEND A REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR:

HEWICK, RODNEY M.

DOC DATE: 01/24/91

ASSIGNOR:

WANG, JACK H.

DOC DATE: 01/24/91

ASSIGNOR:

WOZNEY, JOHN M.

DOC DATE: 01/24/91

ASSIGNOR:

CELESTE, ANTHONY J.

DOC DATE: 01/24/91

RECORDATION DATE: 01/27/92 NUMBER OF PAGES 003 REEL/FRAME 5988/0717

DIGEST :ASSIGNMENT OF ASSIGNEES INTEREST

ASSIGNEE:

GENETICS INSTITUTE, INC.  
A CORPORATION OF DE  
87 CAMBRIDGE PARK DRIVE  
CAMBRIDGE, MASSACHUSETTS

SERIAL NUMBER 7-800364 FILING DATE 11/26/91 ←  
PATENT NUMBER ISSUE DATE 10/00/00

22

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992

See mbo/jhs

GI 5182A  
USSN 07/800,364  
Filing Date 11/26/91  
Group Art Unit \_\_\_\_\_

## ASSIGNMENT

In consideration of good and valuable considerations, the receipt of which is hereby acknowledged, we, the undersigned, Rodney M. Hewick, Jack H. Wang, John M. Wozney, and Anthony Celeste residing at:  
16 Woodcliffe Road, Lexington, MA 02173  
522 Lowell Street, Lexington, MA 02173  
59 Old Bolton Road, Hudson, MA 01749  
86 Packard Street, Hudson, MA 01749 respectively hereby sell, assign and transfer to Genetics Institute, Inc. a corporation of the State of Delaware having a place of business at 87 CambridgePark Drive, Cambridge, in the County of Middlesex and the State of Massachusetts, its successors, assigns and legal representatives, the entire right, title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned on and is entitled

### BONE AND CARTILAGE INDUCTIVE PROTEINS

(GI case no. 5182A) and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for United States Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorize and request the Commissiner of Patents of the United States to issue to said Assignee, the corporation above named, its successors, assigns and legal representatives, in accordance with this assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;

Agree that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and may sue for and recover profits and damages for any and all infringements thereof; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known

REI5988 FAM718

GI 5182A USSN 07/800,364 Filing Date 11/26/91  
Group Art Unit \_\_\_\_\_

and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives;

Authorize my/our attorney to insert hereon \* the serial number, filing date and group art unit of the United States patent application referred to above after the same shall have been made known to such attorney by the United States Patent Office; and

Covenant with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.

Rodney M. Hewick

[L.S.]

Rodney M. Hewick

Jack H. Wang

[L.S.]

Jack H. Wang

John M. Wozney

[L.S.]

John M. Wozney

Anthony J. Celeste

[L.S.]

Anthony J. Celeste

Commonwealth of Massachusetts

Middlesex County S.S. Date 1/24/91

then personally appeared the above named

Rodney M. Hewick, Jack H. Wang, John M. Wozney, Anthony J. Celeste

and acknowledged the foregoing instrument to be his/her free act and deed before me

Ellen M. Zaglakas, NOTARY PUBLIC.

My commission expires on February 18, 1994

Signed Ellen M. Zaglakas

RECORDED  
PATENT AND TRADEMARK  
OFFICE  
JAN 27 1992

\*Insertion of the serial number, filing date and group art unit of the application referred to above was made by me this 24th day of January, 1992.

Ellen J. Kapinos  
Attorney for Applicant(s)

Ellen J. Kapinos

Reg. No. 32,245

REF 5988 FILED 7/19



GI 5182A P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rodney M. Hewick et al  
Serial No.: 07/800,364  
Filed : November 26, 1991  
For : BONE AND CARTILAGE INDUCTIVE PROTEINS

January 24, 1992

Hon. Commissioner of Patents  
and Trademarks  
Box Assignment  
Washington, DC 20231



SEARCHED INDEXED  
SERIALIZED FILED  
JAN 24 1992  
U.S. TRADEMARK OFFICE

RECEIVED

LETTER

SIR:

Enclosed is an assignment of the above-identified application, executed January 24, 1992, to Genetics Institute, Inc., a corporation of Delaware.

Authorization is hereby given to charge the \$8.00 recordation fee and any additional fees which may be required in this regard, and to credit any overpayment, to Deposit Account No. 07-1060. Two duplicate copies of this letter are enclosed.

Respectfully submitted,

*Ellen J. Kapinos*  
Ellen J. Kapinos  
Reg. No. 32,245  
Attorney for Applicants  
(617) 876-1170

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992.

*Ellen J. Kapinos*

115988 FILED 7/17

US14256 02/03/92 07800364

07-1060 140 581

40.00CH

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 24, 1992

See m/z 362

GI 5182A  
USSN 07/800,364  
Filing Date 11/26/91  
Group Art Unit \_\_\_\_\_

## ASSIGNMENT

In consideration of good and valuable considerations, the receipt of which is hereby acknowledged, we, the undersigned,  
Rodney M. Hewick, Jack H. Wang, John M. Wozney, and Anthony Celeste  
residing at:

16 Woodcliffe Road, Lexington, MA 02173  
522 Lowell Street, Lexington, MA 02173

59 Old Bolton Road, Hudson, MA 01749  
86 Packard Street, Hudson, MA 01749 respectively  
hereby sell, assign and transfer to Genetics Institute, Inc. a corporation of the State of Delaware having a place of business at 87 CambridgePark Drive, Cambridge, in the County of Middlesex and the State of Massachusetts, its successors, assigns and legal representatives, the entire right, title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned on and is entitled

### BONE AND CARTILAGE INDUCTIVE PROTEINS

(GI case no. 5182A) and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for United States Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorize and request the Commissioner of Patents of the United States to issue to said Assignee, the corporation above named, its successors, assigns and legal representatives, in accordance with this assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;

Agree that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and may sue for and recover profits and damages for any and all infringements thereof; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known

1115988 NAME 718

GI 5182A . . . USSN 07/800,364 Filing Date 11/26/91  
Group Art Unit \_\_\_\_\_

and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives;

Authorize my/our attorney to insert hereon \* the serial number, filing date and group art unit of the United States patent application referred to above after the same shall have been made known to such attorney by the United States Patent Office; and

Covenant with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.

Rodney M. Hewick

[L.S.]

Rodney M. Hewick

Jack H. Wang

[L.S.]

Jack H. Wang

John M. Wozney

[L.S.]

John M. Wozney

Anthony J. Celeste

[L.S.]

Anthony J. Celeste

Commonwealth of Massachusetts

Middlesex County S.S. Date 1/24/91

then personally appeared the above named

Rodney M. Hewick, Jack H. Wang, John M. Wozney, Anthony J. Celeste  
and acknowledged the foregoing instrument to be his/her free act and deed before me

Ellen M. Zaglakas, NOTARY PUBLIC.

My commission expires on February 18, 1994

Signed Ellen M. Zaglakas

RECORDED  
PATENT AND TRADEMARK  
OFFICE  
JAN 27 1992

\*Insertion of the serial number, filing date and group art unit of the application referred to above was made by me this 24th day of January, 1992.

Ellen J. Kapinos  
Attorney for Applicant(s)

Ellen J. Kapinos

Reg. No. 32,245

59884719



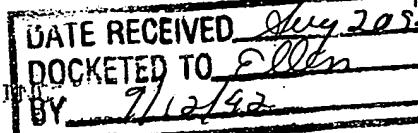
18

UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
800,364	11/26/91	HEWICK	R 5102A

LEGAL AFFAIRS DEPT.  
GENETICS INSTITUTE,  
87 CAMBRIDGE PARK DR.  
CAMBRIDGE, MA 02140



EXAMINER	
FURMAN, K	
ART UNIT	PAPER NUMBER
1814	

DATE MAILED:

08/12/92

9/12/92

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 CFR 1.821 through 1.825 for one or more of the reasons set forth on the attached form "Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/Or Amino Acid Sequence Disclosures," wherein attention is directed to paragraphs 4d and 5.

Any inquiry concerning this communication should be directed to Examiner Keith Furman, Art Unit 1814, whose telephone number is (703) 308-3453.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS  
CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE  
DISCLOSURES

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 CFR §§ 1.821 through 1.825 as follows:

1. This application clearly fails to comply with the collective requirements of §§ 1.821 through 1.825. Applicant's attention is directed to these regulations, a copy of which is attached.
2. This application does not conform exclusively to the requirements of §§ 1.821 through 1.825. The non-conforming material should be deleted. § 1.821(b).
3. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing." § 1.821(c).
4. This application does contain, as a separate part of the disclosure on paper copy, a "Sequence Listing." However, the "Sequence Listing" does not comply with the requirements of §§ 1.821 through 1.825 as follows:
- a. The sequence data does not comply with the symbol and format requirements of paragraphs (b) through (p) of § 1.822. Specifically: \_\_\_\_\_
- b. The "Sequence Listing" does not comply with the location and page requirements of paragraph (a) of § 1.823.
- c. The "Sequence Listing" does not comply with the information requirements of paragraph (b) of § 1.823. Specifically: \_\_\_\_\_
- d. Other: *Sequences to human BMPs in Figure 2 do not comply with the sequence rules*
5. The description and/or claims of the patent application mention a sequence that is set forth in the "Sequence Listing" but reference is not properly made to the sequence by use of a sequence identifier as required by § 1.821(d).
6. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by § 1.821(e).
7. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the computer readable form does not comply with the requirements of § 1.824. Specifically: \_\_\_\_\_
8. A statement that the content of the paper and computer readable copies are the same has not been submitted as required by § 1.821(f).
9. The amendment to or replacement of the paper and/or computer readable copies of the "Sequence Listing" does not comply with the requirements of § 1.825(a) through (c).
10. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable. Applicant must provide a substitute copy of the data in computer readable form accompanied by a statement that the substitute data is identical to that originally filed. § 1.825(d). Specifically: \_\_\_\_\_
11. Other: \_\_\_\_\_

APPLICANT IS GIVEN ONE MONTH FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE ABOVE REQUIREMENTS. Failure to comply with the above requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136. Direct the response to, and any questions about, this notice to the undersigned. A copy of this notice MUST be returned with your response.

For: Manager, Application Processing Division  
(703) 308-1202 or 308-\_\_\_\_\_

Examining Group 18/4  
(703) 308-4216



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

(14)

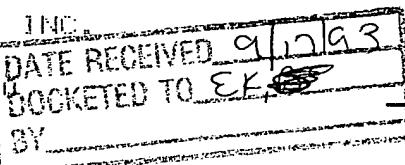
SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
077800, 354	11/26/91	PIERLIER	R 5162A

LEGAL AFFAIRS DEPT.

GENETICS INSTITUTE, INC.

87 CAMBRIDGE PARK DR

CAMBRIDGE, MA 02142



18M2/0903

EXAMINER	
F. O'Donnell, E.	
ART UNIT	PAPER NUMBER
	11

DATE MAILED: 14

09/07/93  
9/14/93

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1.  Applicant's failure to respond to the Office letter, mailed 2-5-93.
2.  Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3.  Applicant's failure to timely file the response received \_\_\_\_\_ within the period set in the Office letter.
4.  Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of \_\_\_\_\_ of the Notice of Allowance.

The issue fee was received on \_\_\_\_\_.

The issue fee has not been received in Allowed Files Branch as of \_\_\_\_\_.

In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.

5.  Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by \_\_\_\_\_ as required in the last Office action.  
 The corrected and/or substitute drawings were received on \_\_\_\_\_.
6.  The reason(s) below.

*Keith R. Pearson*  
KEITH R. PEARSON  
PATENT EXAMINER  
GROUP 1800

FORM PTO-892 (REV. 2-92)			U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		SERIAL NO.	GROUP/ART UNIT	ATTACHMENT TO PAPER NUMBER	10
NOTICE OF REFERENCES CITED			APPLICANT(S)		<i>Hewrich et al.</i>			
U.S. PATENT DOCUMENTS								
*	DOCUMENT NO.	DATE	NAME		CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE	
A	5011691	4-30-91	<i>Oyzenmann et al.</i>		424	423		
B								
C								
D								
E								
F								
G								
H								
I								
J								
K								
FOREIGN PATENT DOCUMENTS								
*	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PP. SPEC.
L								
M								
N								
O								
P								
Q								
OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)								
R								
S								
T								
U								
EXAMINER	DATE							
<i>Walt Fornan</i>	1-28-93							
* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)								

PATENT  
Serial No. 07/800,364 Doc. No. GI 5182A Atty/Sec. EK/DG Date Oct 5, 1994  
Inventor Hewick et al.  
Title DNA Encoding and Methods For Producing BMP-8 Proteins

The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

On Spec. \_\_\_\_\_  
Abstract 1 pp. Preliminary Amendment  
Iter Diskette(s) ✓ 15 pp. Amendment/Response  
listing 825(a) ✓ pp. Declaration/Exhibits  
825(b) ✓ 1 pp. Transmittal Letter (triplicate)  
, P. PTO 948 ✓ pp. Appeal Brief (triplicate)  
Issue Fee  
(ap) ✓ 2pp Notice of Appeal & Fee ✓ 1 6pp Appendix  
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Respectfully,  
Genetics Institute, Inc.

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PATENT  
Serial No. 07/800,364 Doc. No. GI 5182A Atty/Sec. EK/DG Date Oct 5, 1994  
Inventor Hewick et al.  
Title DNA Encoding and Methods For Producing BMP-8 Proteins

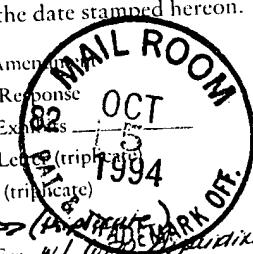
The following has been received in the U.S. Patent and Trademark on the date stamped hereon.

On Spec. \_\_\_\_\_  
claims (1-), Abstract 1 pp. Preliminary Amendment  
✓ 13 pp. Sequence ID Listing/Computer Diskette(s) ✓ 15 pp. Amendment/Response  
✓ 2 pp. Statement re Sequence ID Listing 825(a) ✓ pp. Declaration/Exhibits  
825(b) ✓ 1 pp. Transmittal Letter (triplicate)  
pp. Declaration/Power of Attorney  
✓ 3 shts. Informal/Formal Drawings 1p. PTO 948 ✓ pp. Appeal Brief (triplicate)  
pp. Assignment & Fee ✓ Issue Fee  
✓ 1 pp. Extension of Time & Fee (duplicate) 2pp Notice of Appeal & Fee ✓ 1 6pp Appendix  
pp. Information Disclosure Statement & Fee ✓ 2pp Drawing Transmittal (duplicat)e  
with PTO-1449 and \_\_\_\_\_ references

The Patent and Trademark Office is respectfully requested to place its stamp on this postal card  
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Express Mail Label No. RB 793 967 900 US



Form PTO-1449			Atty. Docket No. GI 5182A		Serial No. 07/800,364		
INFORMATION DISCLOSURE STATEMENT			Applicant(s) Rod Hewick et al.				
			Filing Date November 26, 1991		Group 1814		

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	*BE	WO 91/18047	11/28/91	WIPO			

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Examiner	Date Considered
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Form PTO-1449  INFORMATION DISCLOSURE STATEMENT			Atty. Docket No. GI	5182A	Serial No. 071	800,364
			Applicant(s)	Rod Hewick et al		
			Filing Date Nov. 26, 1991	Group 1814		

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Examiner	Date Considered
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